PYELONEPHRITIS

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PREFACE

Pyelonephritis is one of the most important present problems of modern medicine. Only within recent years has its seriousness been generally recognized. Studies of the pathology and the clinical course of pyelonephritis have made clear certain facts that previously were not appreciated and, although progress has been made in a better understanding of this disease, many of its problems remain unsolved.

When pyelonephritis is acute its symptoms are characteristic, diagnosis usually is evident, the response to modern treatment is excellent, and mortality is low. Acute pyelonephritis is no longer the problem of past years. Chronic pyelonephritis is different. Its symptoms often are vague and misleading, diagnosis may be difficult, treatment is unsatisfactory, and renal damage can be so severe that the result is uremia and death.

Recent literature concerning pyelonephritis has been extensive. Opinions expressed have varied to such an extent that it is apparent that there are many things about this condition that still are unknown. These many reports, however, have emphasized the frequency and seriousness of pyelonephritis and have made clear one important fact—that every effort should be made to prevent the disease from becoming chronic. This means early and adequate treatment of acute pyelonephritis.

This book describes the background of pyelonephritis and sum-

marizes what we now know about the disease. The development, anatomy, and physiology of the kidneys are presented The pathology, symptoms, diagnosis, and treatment of acute and chronic pyelonephritis are described. Separate chapters are devoted to pyelonephritis in infancy and childhood, in pregnancy, in diabetes, and to the association of pyelonephritis and hypertension. Much of the text is based upon our own experience with pyelonephritis at the Massachusetts General Hospital.

The book should be useful to students, general practitioners of medicine, and to the occasional internist who may know less about this disease than I. It is written from the point of view of a urologist

My sincere thanks go to my secretary, Miss Frances Schwab, for her meticulous preparation of the manuscript, to Donald C. Withee of the photographic department of my hospital for his help in preparing the illustrations, and to Dr. Wyland F. Leadbetter for valuable suggestions.

F. H. C.

CONTENTS

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PYELONEPHRITIS

A Russian-born laborer of 48 came to the hospital with the complaint of increasing exertional dyspnoea for six months He had been perfectly well until three years before when severe generalized headaches developed. However, he had continued to work until the recent shortness of breath made this impossible. Six weeks ago his appetite failed, he was nauseated, vomited frequently, and became more and more drowsy Never had there been any urinary symptoms

Upon admission, he was severely dyspnoeic. The breath was uremic His blood pressure was 200/110 Moist rales were present at both lung bases and the heart was enlarged The neck veins were distended and there was ankle edema He obviously was in congestive heart failure. Eye grounds, narrowed retinal vessels and flame-shaped hemorrhages

Significant laboratory findings were a cloudy urine of low specific gravity (1 008) with albumin 4 plus and many red and white blood cells (R. and W B C.) and granular casts in the sediment Urine culture, no growth Nonprotein nitrogen (N P N),



Fig. 1. Severe bilateral chronic pyelonephritis with hypertension. Death in uremia Marked destruction of renal architecture with scarring, chronic inflammatory cellular infiltration and tubular dilatation with proteinaceous casts. Photomicrograph Low power.

76 mg. per cent, CO_2, 21.5 m.eq ; Cl, 109 m eq.; Ca, 9.0 m.eq.; P, 6.1 m.eq , hemoglobin (Hgb.), 10.5 gm. Chest x-ray: cardiac enlargement and pulmonary edema.

His prognosis was considered to be grave, but he improved with digitalis and left the hospital, although the N.P.N. had risen to 82 mg. per cent. He became progressively worse with nausea, anorexia, muscular twitching, and disorientation. Within a month he was readmitted in advanced uremia, was comatose, and in 12 hours was dead.

At postmortem examination there was severe chronic pyelonephritis, cardiac hypertrophy, fibrous pericarditis, bilateral hydrothorax, and secondary parathyroid hyperplasia (Fig. 1).

This is the short history of renal failure, uremia and death from chronic pyelonephritis. The disease was insidious in nature, no urinary symptoms had preceded its onset, treatment was of no

avail, and an accurate diagnosis was made only at autopsy *This was chronic pyelonephritis*

The Past History of Pyelonephritis

For centuries pyelonephritis has been a common disease. Only within recent years, however, has it been generally appreciated that pyelonephritis, acute or chronic, has become one of the foremost problems in medicine At present, the disease is recognized as an infectious process that involves not only the renal pelvis but chiefly the parenchyma of the kidney and particularly the interstitial tissues In 1929 Wilson and Schloss (1) called attention to the fact that "pyelitis" was really a true suppurative lesion of the interstitial tissues of the kidney This statement was based upon a postmortem study of 49 infants who had had pyuria Pathological examination of the kidneys showed inflammatory foci in the interstitial tissues often adjacent to small blood vessels. Pyelitis obviously was a misnomer; the more correct term was pyelonephritis.

The contracted kidneys of chronic pyelonephritis had been described by Löhlein in 1917 (2) The natural history of the disease was suggested by many authors (3-5).

The publication of the clinical observations of Longcope and Winkenwerder (6) in 1933 built the foundation for the appreciation of the real character of chronic pyelonephritis. These authors emphasized the importance of recognizing this disease in its early stages, particularly in childhood, during the puerperium, and in obstructive lesions of the urinary organs Their description of a small group of cases applies well today, particularly regarding the frequent occurrence in young women of recurring attacks of urinary infection accompanied by lumbar pain, cardiac hypertrophy, retinitis, nitrogen retention, occasionally elevated blood pressure, scanty urinary findings, pyelographic changes, uremia, and death.

Longcope observed that certain patients who died in uremia, supposedly from chronic Bright's disease, had, at autopsy, chronic pyelonephritis with shrunken kidneys and irregularly dilated renal pelves He also noticed that some children who gave a

history of recurrent attacks of "pyelitis" and who died in uremia had chronic pyelonephritis. He realized that chronic pyelonephritis was different from the usual conception of Bright's disease and he emphasized the importance of chronic pyelonephritis as a cause of renal failure.

Most of Longcope's patients (*7 of 9*) *were young women whose* symptoms before renal failure often had been vague and slight but of long duration. Frequently, the history was one of poor health for many years with recurrent episodes of fever. Lumbar pain and cloudy urine accompanied these episodes. During childhood or adolescence pus or albumin had been present in the urine. The symptoms presented when these patients were first seen by a physician were those of renal failure. Medical advice was sought because of headache, loss of weight, lassitude, dyspnoea, nausea and vomiting, epistaxis, lumbar pain, and, at times, convulsions. *All were signs of renal insufficiency.* Anemia, sometimes severe, usually existed. Retinitis with hemorrhagic exudates often was present. Edema occurred only when there was cardiac failure. Cardiac enlargement or an elevated blood pressure were not always present but hypertension existed in over one-half of Longcope's cases. Urinary abnormalities occurred in all. Large quantities of urine were passed with the specific gravity fixed between 1.006 and 1.012. Only moderate traces of albumin were found and leukocytes almost always were present with few or no hyaline casts. *Escherichia coli* was the commonest organism found by culture. Distinct renal abnormalities were present in these cases as demonstrated by retrograde pyelography. The renal pelves were irregularly deformed and often slightly dilated. The calyces were distorted and blunted.

That serious renal damage was present in Longcope's small series was evident by renal function tests. Excretion of phenolsulfonephthalein often was less than 20 per cent. The nonprotein nitrogen usually was elevated and the urea clearance tests were lower than normal.

Five of Longcope's 9 patients died in uremia. At autopsy, the kidneys were smaller than normal, scarred, and distorted. The renal pelves were slightly dilated and inflamed in varying degrees.

On microscopic examination, areas of inflammation were present with marked replacement of normal kidney tissue by fibrosis.

It is evident that these early cases so well described by Longcope had advanced chronic pyelonephritis with considerable degrees of renal damage His observations clearly showed that certain patients who died in uremia, supposedly from chronic Bright's disease, had chronic pyelonephritis. He also observed that some children who died in uremia, after a history of persistent so-called "pyelitis," had chronic pyelonephritis (7). Longcope's observations were an important contribution and an accurate description of chronic pyelonephritis as it exists today.

During the past thirty-odd years a great many authors have written about pyelonephritis Certain communications in this mass of literature mark the progress that has been made in a better understanding of pyelonephritis Although these studies have served to emphasize the frequency and importance of this disease and to give a clear picture of the pathological changes in the kidney, there still remain many unsolved problems.

In 1927 Braasch and Cathcart (5) made a study of 251 patients with chronic bilateral pyelonephritis. They emphasized the fact that symptoms often were vague or lacking and they described the typical pyelographic deformities that existed. In their experience about one-third of these patients recovered, one-third were considerably improved, and one-third were not helped by treatment Patients who had foci of infection removed fared better as a group than those in whom this was not done. Chown (3) in a study of pyuria in infants of two years of age or less also called "pyelitis" a misnomer since it seldom or never occurred without involvement of the kidney itself

In 1929 Barash (8) favored an ascending route to the kidney for pyelonephritis in children and found *E. coli* the most frequent infecting organism He also believed that focal infections were important contributing factors in etiology In the same year Scott (9) reported 82 cases of blood stream infections following urological procedures The urethra was said to be the portal of entry in 80 per cent The mortality in these cases was 18 per cent and the commonest organism isolated was *E coli* Bacteremia with

chills following urethral instrumentation with positive blood cultures within a few minutes was reported also by Barrington and Wright (10).

At this time Campbell and Lyttle (11) in a report of 74 cases of ureteral obstruction in infancy, with pyuria usually the only diagnostic sign, called attention to the importance of urinary stasis as a predisposing and perpetuating cause of urinary tract infection. Ureteral obstruction was present in nearly 2 per cent of 2420 autopsies on pediatric cases.

The importance of an early recognition of pyelonephritis in children was stressed by Butler and Lanman in 1937 (12). They reported chronic pyelonephritis as a primary cause of death in about 2 per cent of 2043 autopsies, 63 per cent being under 2 years of age. Well over one-half of their children had some anatomical malformation of the urinary tract. The high incidence of pyelonephritis in children was emphasized along with its seriousness in infants with or without anatomical abnormalities. Chronic pyelonephritis, they stated, was the commonest cause of renal insufficiency with uremia. *A relationship between chronic pyelonephritis and hypertension was shown to exist.*

In a review of over 500 cases of pyelonephritis at the Mayo Clinic, Braasch (13) stated that the disease often is so mild and symptoms so vague that the condition is recognized only on urinalysis with culture and gram stains of the urinary sediment. About 20 per cent of his cases were said to recover without treatment Secondary calculi formed in only 28 of 526 cases and their removal seldom was necessary. He also stressed the necessity of treating foci of infection and the importance of early and adequate treatment of acute infections.

The late effects of acute "pyelitis" in girls were reviewed by Wharton *et al* (14) in a follow-up study of 30 patients. Nine had had one attack of "pyelitis" on an average of 13 years previously and, although 3 showed no abnormality, 9 had definite pathological changes in the urinary tract, although these girls were in good health. When there had been repeated acute attacks during the previous 10 years no permanent damage was found in any, but when these attacks were associated with persistent patho-

logical changes in the urinary tract all but 2 of 11 had continued symptoms. One had renal insufficiency, one ended with a shrunken, functionless kidney, and in 57 per cent there were definite urinary abnormalities The authors stated that the effects of "pyelitis" often were more grave than had been expected

In a study of 172 cases of chronic pyelonephritis by Nesbit and Conger (15) the diagnosis was made in 80 per cent by characteristic pyelographic changes or by pathological examination. Pyelograms were normal in 20 per cent. Girls predominated three to one and women two to one, but in the fifth to eighth decades men and women were even Symptoms varied from 3 months to 20 years with cystitis the initial symptom in 61 per cent. It was felt that the diagnosis could have been made earlier in 84 per cent and that earlier treatment might have helped Some degree of renal impairment existed in 75 per cent and was marked in 25 per cent With progressive degrees of renal impairment, mortality increased and the response to treatment was poorer. Many cases, however, lived for years with little effect on renal function, blood pressure or pyelographic changes At times, though, the disease took a rapid and fulminating course. After treatment, 37 per cent showed no great change, 34 per cent were improved in health and symptoms, but only 3 per cent became free of symptoms and subsequently had repeatedly normal urines The authors felt that all patients with acute pyelonephritis should be treated, not only until they were symptom free, but until the urine was free of bacteria on many examinations.

Although the small contracted kidneys of advanced chronic pyelonephritis had been studied and reported early, particularly by German authors (2, 16), the studies of Weiss and Parker (17) were largely responsible for the recent interest in pyelonephritis. They described the vascular lesions of pyelonephritis as a feature of the disease since these were considered to be a factor in the production of hypertension The relationship between renal and vascular changes and hypertension was as follows. (a) A mild degree of arteriosclerosis of both kidneys usually was associated with normal blood pressure. (b) A severe degree of arteriosclerosis in unilateral pyelonephritis might or might not be so associated.

(c) A severe degree of arteriosclerosis of both kidneys practically always was associated with severe hypertension. They considered that pyelonephritis was responsible for 15 to 20 per cent of cases of malignant hypertension.

Changes in the glomeruli with atrophy and hyalinization associated with pyelonephritis were described by Kimmelstiel and Wilson (18) in kidneys that showed arterial or arteriolar sclerosis.

With the stimulus provided by Weiss and Parker, more attention was directed to the pathology of pyelonephritis, combined with experimental work, in an effort to trace its origin. Unilateral pyelonephritis in rabbits was produced by Mallory *et al.* (19) by the intravenous injection of colon bacilli after partial ligation of one ureter Acute pyelonephritis, similar to that in man, was produced in the partially obstructed rabbit's kidney in 25 per cent of the experimental animals At the end of 2 months, the obstructed kidneys were markedly contracted and pale gray in color. No extensive pyelonephritis was found in the unobstructed kidney. These experiments demonstrated that urinary obstruction was a very important factor in the development of bloodborne pyelonephritis

It was shown also by Bell (20) that the obstructive form of pyelonephritis was about 12 times as common as the nonobstructive type in autopsy material. In 32,360 autopsies, hydronephrosis was present in 1229 and pyelonephritis was present in 60 per cent.

The relationship between renal ischemia and hypertension was provided by the experiments of Goldblatt *et al.* in 1934 (21) by causing renal ischemia in dogs through narrowing the lumens of both renal arteries by means of adjustable clamps Permanent hypertension was produced (22). If normal renal tissue was present, these experiments were not successful. There were two possibilities. As a result of renal ischemia a pressor substance was produced, but if a normal kidney was present this substance had no effect. The other possibility was that the pressor substance was neutralized by something produced by the normal kidney.

As Boyd (23) pointed out, in spite of this experimental evidence it has been shown that unilateral renal ischemia in man may result in hypertension and that pyelonephritis and hypertension

are associated and that occasionally in unilateral lesions the hypertension is cured by nephrectomy.

Homer Smith (24) took a cautious attitude in this respect. He felt that unilateral renal pathology might be the cause of hypertension in rare instances but that the 19 per cent of successes from nephrectomy and the fact that most urological disease did not cause hypertension, left a reasonable doubt about this hypothesis If bilateral renal disease is present, as is usually so in advanced hypertension, nephrectomy may shorten life by the removal of an important fraction of total available renal function.

Since the production of hypertension by the pyelonephritic kidney is far from being completely understood, it can be stated with considerable emphasis that a careful evaluation of all available facts should be made before nephrectomy is considered

It is well established that pyelonephritis is the result of invasion of the kidney by bacteria The initial infection may be the beginning of a disease that can lead to renal failure, uremia, and death *The methods by which bacteria reach the kidneys have* been debated for years. In obstructive lesions of the lower urinary tract with reflux of infected urine up the ureters the ascending route is obvious The chills and fever with positive blood cultures that sometimes follow urethral instrumentation indicate that bacteria may reach the kidney by the blood stream A spread of infection to the kidney from organs in the pelvis by the lymphatics has been a controversial subject but since most investigators have been unable to demonstrate lymphatic pathways by which this can occur such a route seems unlikely

Acute pyelonephritis is readily recognized by its characteristic symptoms of chills, fever, loin pain, painful and urgent urination, and kidney tenderness Modern therapy quickly relieves these patients but each attack of acute pyelonephritis may be serious because of the possible consequences. Repeated acute episodes mean that the initial infection has not been completely eliminated or that reinfection has occurred In any event, repeated acute episodes of renal infection mean that progressive renal damage is taking place with the possibility of eventual renal failure.

Unlike acute pyelonephritis, chronic pyelonephritis often exists

without characteristic symptoms. Here, there may be little or no evidence of active infection and no local symptoms. Pallor, easy fatigability and loss of weight may be the only symptoms. A diagnosis is made largely by laboratory examinations. Large volumes of urine are passed with a low specific gravity, mild proteinuria, and with few leukocytes in the sediment. Pyuria often is intermittent and urine cultures may show no growth. However, repeated cultures and examinations of the stained sediment often reveal the presence of active infection. Pyelography may aid in the diagnosis by characteristic changes in the renal calyces and ureters but the pyelograms often have been normal in patients with chronic pyelonephritis.

It is agreed that acute pyelonephritis should be effectively treated by the appropriate chemotherapeutic agent after the infecting organisms have been identified and sensitivity tests have been done. The treatment of chronic pyelonephritis many times is unsatisfactory and intelligent therapy should take into consideration any complications that favor infection, the duration of the disease, arterial status and renal function. Pyelonephritis in diabetics often is impossible to cure. If hypertension exists, treatment is quite likely to be unsatisfactory.

From the foregoing it is apparent that progress has been made in a clearer understanding of pyelonephritis. Milestones in progress were Longcope's early and accurate descriptions of the disease. His reports made a great impression upon internists by differentiating chronic pyelonephritis from Bright's disease as a cause of failing renal function, uremia, and death. He pointed the way toward more accurate diagnosis and, eventually, to more intelligent treatment. Braasch brought to the attention of urologists the importance of pyelonephritis by his careful and comprehensive studies at the Mayo Clinic. Previous to this, the serious implications of this disease were scarcely appreciated by most urologists. The frequency with which pyelonephritis occurs in infancy and childhood and the high incidence of obstructive urinary tract lesions were demonstrated by Campbell. The seriousness of the condition in children and the relationship between hypertension and chronic pyelonephritis were pointed out by

Butler. The careful correlation between the clinical course of pyelonephritis and the pathological changes that were present, as portrayed by Weiss and Parker, gave impetus to the more careful study of patients with chronic renal disease and they demonstrated the association of chronic pyelonephritis with hypertension. Mallory's work resulted in a better understanding of the methods by which renal infection takes place. A great contribution toward the correlation of some types of hypertension and renal disease resulted from the experiments of Goldblatt. Homer Smith has tried to put the relationship between hypertension and unilateral renal disease on an even keel.

All of these investigators have added to our knowledge of this serious disease, pyelonephritis.

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2

THE KIDNEY: EMBRYOLOGY, ANATOMY, AND PHYSIOLOGY

Any discussion of pyelonephritis calls for a description of the embryology, anatomy, and physiology of the kidney The adult human kidney is the result of three stages of development in the embryo the pronephros, mesonephros, and metanephros The pronephros and mesonephros degenerate, and the metanephros persists as the functioning adult kidney

Embryology

In the embryo, the pronephros develops late in the third week of life as about seven pairs of tubules derived from embryonic nephrotomes One end of each tubule drains the celomic cavity and the other end opens into the pronephric duct which empties into the cloaca. The pronephros probably does not function in the human embryo and its tubules degenerate The pronephric duct persists as the wolffian or mesonephric duct (Fig 2)

The mesonephros, or wolffian body, appears in the fourth week of embryonic life It is developed from the same mass of meso-

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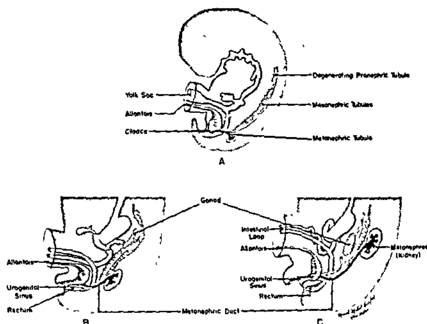


FIG 2 Development of the kidney A Pronephros (fifth week). B. Mesonephros (seventh week) C. Metanephros (eighth week). (After Patten) From Colby, F. H Essential Urology, Ed 3. The Williams & Wilkins Co , Baltimore, 1956

nephric tissue as the pronephros. Mesonephric tubules connect with a mesonephric duct. A primitive glomerulus is developed by the blind end of a tubule forming a cup about a knot of blood vessels that arise from the dorsal aorta. The mesonephros provides the embryo with a temporary excretory organ. The mesonephric tubules degenerate by the fourth month of life, but certain of the tubules persist to form the paradidymis and the aberrant and efferent ductules of the male testis. The main mesonephric duct persists as the vas deferens.

The *metanephros, or adult kidney, develops during the growth* and degeneration of the mesonephros. The distal or collecting portion of the kidney forms by an outgrowth of each mesonephric duct near the cloaca (Fig. 3). The first portion of the metanephros



Fig 3 Metanephros Development of the adult kidney and ureter (After Cabot) From Colby, F H Essential Urology, Ed 3 The Williams & Wilkins Co , Baltimore, 1950

enlarges and lengthens to form the ureters At their distal ends, the ureteral stalks enlarge to make the renal pelvis Major and minor calyces develop by further growth and subdivision and collecting tubules grow from the minor calyces of the newly formed renal pelvis. The collecting tubules branch and subdivide and constitute the pyramidal masses which are composed of tubules that radiate from the calyces

The second portion of the kidney, the renal parenchyma, develops by lengthening of the embryonic ureter and its pushing into a mass of nephrogenic tissue which surrounds the dilated end of each ureter (Fig 4) Secretory tubules are formed which connect with the collecting tubules The blind end of each tubule becomes cup-shaped and envelops a knot of capillaries This is to form a glomerulus A thin capsule made from the lining of the tubule covers the capillary tuft and lines the cavity in which it lies This is Bowman's capsule The space within the capsule is continuous with the tubular lumen. The tubules elongate, become convoluted and finally connect with collecting tubules The arrangement is such that fluid passing through the capillaries of the glomerular tuft drains from the capsular space down the tubules to the calyces and to the renal pelvis. The functioning renal unit or nephron thus is completed (Fig 5)

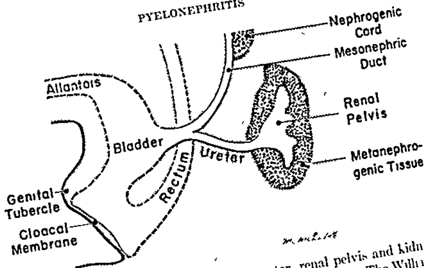


FIG. 4 Further development of the ureter, renal pelvis and kidney (After Arey) From Colby, F H. Essential Urology, Ed. 3 The Williams & Wilkins Co, Baltimore, 1956

Gross Anatomy

Each normal adult kidney averages about 150 gm. in weight. In cut sections of the adult kidney, the renal papillae are visible situated at the end of each cupped minor calyx (Fig. 6). Each papilla is at the apex of a renal pyramid. The pyramids form the medulla of the kidney The renal cortex lies at the base of the pyramids and on cut sections is lighter in color and composed of radial striations made up of straight tubules that connect with the tubules of the medulla. Between the striations the glomeruli appear as tiny red points.

Renal Blood Supply

In the early weeks of life, the renal blood supply is derived from the iliac vessels As the kidney reaches its high position during the third month in the embryo, these blood vessels are replaced by arteries that arise from the abdominal aorta. This explains some of the vascular anomalies of later life (1).

The main arteries of the kidney arise from the aorta and ente[r] the renal hilum. Each artery divides into several branches th[at] enter the renal substance between the branches of the renal ve[in]

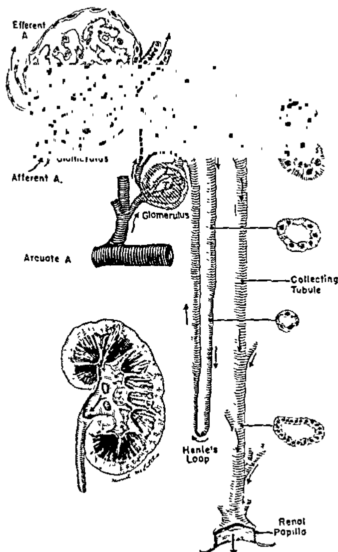


FIG 5 Diagram of a nephron. (After Smith, H W) From Colby, F. H Essential Urology, Ed 3 The Williams & Wilkins Co, Baltimore, 1956

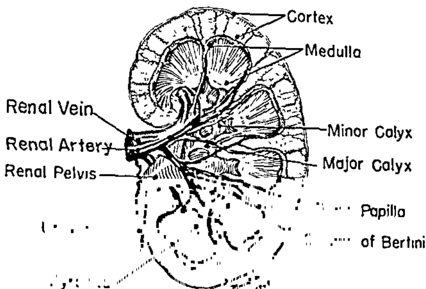


FIG 6 Longitudinal section through the adult human kidney. From Colby, F H Essential Urology, Ed. 3 The Williams & Wilkins Co, Baltimore, 1956

in front and the pelvis of the kidney posteriorly. From these branches of the main arteries interlobar arteries radiate to the boundary of cortex and medulla where they branch as arcuate arteries. The arcuate arteries arch across the bases of the renal pyramids. Branches from the arcuate arteries are the interlobular arteries which extend through the renal cortex. Their fine branches enter the glomerular tufts. The capillaries of the glomeruli unite to form a single afferent blood vessel and a smaller efferent vessel. The efferent artery leaves the glomerulus and divides into small branches that travel through cortex and medulla among the convoluted and straight tubules. Veins accompany the arteries. The interlobar veins emerge from the renal hilum and empty into the renal veins.

Lymphatics

Lymphatic channels in the human kidney seem to be of two groups (Fig. 7). One group begins in the renal cortex and follows

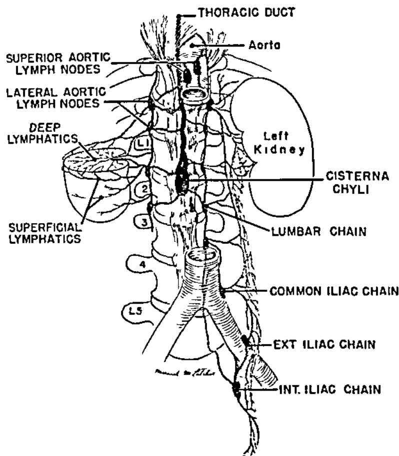


FIG 7 Lymphatics of the kidney and ureter From Colby, F H Essential Urology, Ed 3 The Williams & Wilkins Co, Baltimore, 1956

the interlobular vessels toward the junction of cortex and medulla The other group starts at the renal papillae and joins the cortical system Large trunks then follow the arcuate and interlobar blood vessels and emerge at the renal hilum These lymph channels then, as six to eight trunks, course along the vascular pedicle to empty into the *cysterna chyli* and the *thoracic duct* Through these

channels infected material can readily enter the blood stream (2). In Rawson's (3) description, it was said that especially noteworthy were the lymphatic vessels which lay in close proximity to large thin-walled venous channels that are prominent particularly in the outer half of the renal cortex. In serial sections studied, these vessels appeared to be part of the interlobular veins which in this region are exceptionally large and thin-walled. *Could this be a route by which the kidney becomes diffusely infected as in recurring or chronic pyelonephritis?*

Physiology

The chief function of the kidney is to regulate and control the volume and composition of extracellular body fluids. To keep these fluids within a constant composition is vitally important. This complicated task is accomplished by glomerular filtration, followed by regulated absorption of water and other substances from the filtrate by the tubules and to some extent by tubular excretion The constant levels of the various electrolytes, potassium, sodium, chloride, and others in the plasma and interstitial spaces, depend upon adequate renal function.

The plasma maintains a remarkably constant structure that varies even under extreme conditions within very narrow limits. Because of the ability of the kidney to secrete large amounts of dilute urine or small amounts of concentrated urine the water content of the plasma varies but little. The kidney is able to remove various inorganic compounds in varying amounts and to maintain them in the plasma at precise levels. Plasma constituents that are important, such as glucose, proteins, hormones, and amino acids, are carefully conserved by the kidney. The regulation of the pH of the plasma, or of the acid-base equilibrium of the body fluids, is under renal and respiratory control with the renal assignment a large one. Any variation from a pH of the plasma from 7.4 may be serious. The complex adjustments that are involved in the acid-base balance of the blood depend upon the preservation of a constant total fixed base. This is important because the total fixed base concentration determines the osmotic

value of the plasma and plasma acid must be entirely covered by fixed base.

One important function of the kidneys is to form ammonia. Ammonia used in the excretion of acids in the urine saves fixed base. Probably, ammonia is formed in the distal tubules of the kidney. Since the reaction of the urine can vary from pH 5.0 to pH 8.0 the kidney has considerable latitude in excreting either acids or alkalies. If the urine has a pH of about 5.0 no bicarbonate is excreted and other acids are excreted with less base than neutralizes them in the blood. Plasma base, therefore, is conserved.

Renal function may be disturbed by many factors such as obstructive lesions, disturbances of the blood supply or infections. The ability of the kidney to meet the complex requirements thrown upon it and to perform its functions properly depends upon the structural integrity of this important organ. It is apparent that repeated episodes of acute infection or the ravages of chronic infection with destruction of nephrons limit the ability of the kidney to function as it should.

If the kidneys are diseased badly, their ability to produce ammonia and to control urinary pH is impaired and their ability to excrete acid and to conserve base is lessened. This favors the development of acidosis. The inability of the kidney to excrete larger amounts of base as bicarbonate by raising the pH of the urine limits its ability to protect the patient from alkalosis if alkali is ingested, for the kidney will not remove fixed base to compensate for alkalosis since this would deplete plasma base. The kidney, therefore, is required to regulate the use of fixed base in the construction of urine.

Regardless of the etiological factors—obstructive lesions, generalized disease, circulatory disease, metabolic disturbances, or infection—renal insufficiency results from a reduction in the number of functioning renal elements or from an inability of the nephrons to function properly. The mechanism for the regulation of acid base then is disturbed. With a reduction of the kidney's filtration capacity, it may be unable to excrete adequately substances that normally are present in the plasma in small amounts,

such as calcium, potassium, magnesium, phosphate, sulfate and nonprotein substances such as urea, uric acid and creatinine. If the kidney is damaged it also may be unable to conserve substances that are normally present in the plasma in relatively high concentrations, such as water, sodium, and chloride. Impairment of tubular function results in the inability of the kidney to control the plasma concentration of these substances.

Renal insufficiency may be apparent by abnormalities of the blood and urine. These include changes in reaction, volume, specific gravity, and composition. Abnormalities of the blood chiefly are those that result from the retention of substances that normally are eliminated.

The Urine

Normal urine has a pH between 5.0 and 7.0 with a mean of 6.0. Urinary pH largely is determined by the proportions of di-basic phosphate and mono-basic phosphate. The kidney alters the proportions of those two substances to form a urine of about pH 6 0 from blood which has a pH of 7.4. The acidity or alkalinity of the urine varies with diet and with the ingestion of acid or alkaline substances. In health, the normal adult excretes 1000 to 1800 ml of urine daily. The amount varies with fluid eliminated by the lungs, skin and intestinal tract, but as a rule 40 to 60 per cent of the total fluid intake is excreted by the kidneys. Normally, the amount excreted during the day is two to four times that excreted at night. If the kidneys are diseased, however, the night volume may exceed the day volume.

The excretion of abnormally large amounts of urine may be an early sign of renal damage, whereas the excretion of abnormally small amounts may be a late sign of renal insufficiency. Total suppression of urine excretion occurs in only the severest degrees of renal damage.

Normally, the specific gravity of the urine varies between 1 015 and 1 025 and varies inversely with urine volume. Inability to concentrate urine above 1.010 is evidence of severe renal disease. The specific gravity of the urine depends chiefly upon the concentration of urea and chlorides

Albuminuria commonly is a sign of renal disease, the protein of the plasma passing through the glomerulus. Casts are formed when part of the protein becomes molded within the renal tubules.

Tests of Renal Function

There are two kinds of tests to determine renal function (a) those that provide a gross estimation of renal efficiency, and (b) those that give more precise information of kidney function. The first group of tests are those that are commonly used in the clinical study of the diseased kidney These are the ability of the kidney to concentrate solids, the phenolsulfonephthalein or P S P test, the determination of nonprotein or urea nitrogen in the blood serum, the indigocarmine test and pyelography after the intravenous injection of one of the many organic iodine preparations. More accurate information regarding renal function is obtained by clearance tests—urea clearance and inulin and diodrast clearances.

Urine concentration test The inability to concentrate solids maximally may be an early indication of renal insufficiency If a normal individual restricts fluids for 12 hours the urine specimens voided at hourly intervals have a specific gravity of 1 025 to 1 032 Inability to concentrate above 1 020 is an evidence of defective tubular reabsorption

Phenolsulfonephthalein test The P S.P test measures the ability of the renal tubules to excrete the dye In normal individuals, 30 per cent is excreted in the first 20 minutes and at least 55 per cent at the end of one hour. Fractional determinations, every 15 or 20 minutes, give a better estimation of renal function than a two-hourly urine collection

Nonprotein and blood urea nitrogen In individuals with normal kidneys, the concentration of nonprotein nitrogen in the blood serum does not exceed 35 mg per cent. The normal values for urea nitrogen in the blood serum are 10 to 28 mg per cent. Values higher than this may indicate serious renal damage There are other conditions, however, in which nitrogen retention may exist temporarily because of transient renal impairment An example of this is the following

A 9-year-old girl was admitted to the Massachusetts Gene Hospital because of persistent vomiting and fever for one week. S was seriously dehydrated and drowsy. Physical examination othe wise was not remarkable.

She voided small amounts of urine with a specific gravity of 1.00 to 1.010 The urine contained one plus albumin; many W.B C. and bacteria were in the sediment. Culture, *E coli*. The N.P.N. was 78 mg per cent Temperature and leukocyte counts were elevated. After intravenous glucose and saline solution the N.P.N. fell to 16 mg per cent. The urea clearance was then normal and she was able to concentrate solids normally. By intravenous pyelography both kidneys were normal Her acute pyelonephritis was effectively treated.

In this instance, renal function was temporarily deranged enough to cause nitrogen retention because of acute renal infection and severe dehydration

These tests give only an approximate appraisement of glomerular function and they may have normal figures in the presence of a considerable degree of renal damage.

Intravenous urography. Various organic iodine preparations injected intravenously are sufficiently concentrated by the kidneys to be visible by x-ray examination. In this way, qualitative information regarding renal function may be secured If the kidneys cannot concentrate to a specific gravity above 1.014 these compounds usually are not concentrated sufficiently to be of much help. Delayed films, an hour or more after the dye is given, however, may be informative especially when obstructive lesions are present.

Indigocarmine. The intravenous injection of indigocarmine at the time of cystoscopic examination gives very useful information regarding the separate function of each kidney. Degrees of renal impairment can be roughly estimated by the time of appearance of the dye from each ureteral orifice and by the intensity of the dye.

Clearance tests. Urea is removed from the plasma by filtration. Urea clearance is defined as the volume of blood that one minute's excretion of urine suffices to clear of urea. The urea clearance test

gives a fairly good measure of glomerular filtration. Inulin clearance is useful to determine the rate of formation of glomerular filtrate since inulin is excreted entirely through the glomerular membrane and is not excreted or reabsorbed by the tubules. Diodrast clearance measures effective renal blood flow and provides information regarding maximal tubular activity (4).

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3

INCIDENCE OF PYELONEPHRITIS

Many have commented upon the frequency with which p[illegible] lonephritis occurs both clinically and as a pathological en[illegible]. This disease is a well known complication of obstructive le[illegible] of the urinary organs such as prostatic enlargements, benign or malignant, narrowings of the urinary passages from the kid[illegible] to the urethral meatus, calculous disease, neoplasms, and ce[illegible] lesions that affect the neuromuscular mechanism of the bl[illegible]. Congenital abnormalities in infancy and childhood pro[illegible] fertile field for renal infection. Mechanical factors, therefore [illegible] of great importance in the genesis of pyelonephritis. Such [illegible] normalities account for its greater frequency in the early years of life and in the elderly.

The tendency for pyelonephritis to follow urethral instrumen[illegible] tion and operative procedures upon the urinary organs is [illegible] known. But how often catheterization or the presence of in[illegible] urethral catheters are responsible for renal infection is debata[illegible]. Long periods of urinary drainage by catheters or drains unq[illegible] tionably are responsible for some instances of pyelonephritis [illegible]

perhaps the dangers of simple catheterization have been over-emphasized

Certain generalized diseases favor the onset of pyelonephritis In diabetics, its prevalence is well known Its high incidence in pregnancy often has been remarked upon It is a frequent complication of gout and hyperparathyroidism, particularly when these conditions result in calculous formation

It was said by Keefer (1) that pyelonephritis, acute and chronic, is the number one problem today in infectious disease caused by bacteria and that these cases are increasing in frequency He believed that chronic bilateral pyelonephritis with contracted kidneys was the commonest renal lesion as a cause of uremia This has had the substantiation of many authors in the past

Pyelonephritis has been considered to be the most common disease of the kidney by many (2, 3, 4, 5) Campbell (6) said that urinary tract infections in children under two years of age probably outrank any other form of infection

The frequency of pyelonephritis associated with various types of anatomical lesions of the kidney treated by nephrectomy was reported by Jackson *et al* (7) as follows nephrolithiasis, 85 per cent, hydronephrosis, 83 per cent, congenital anomaly, 50 per cent, carcinoma, 7 per cent All of these are obstructive lesions

The incidence of pyelonephritis in neurogenic bladders diabetes, and lesions causing urinary obstruction was high according to Beeson (8) Derow (9) stated that during the diaper stage fecal contamination of the urinary tract could occur and that pyelonephritis in the early years of life was more common in females than in males This was attributed to the short urethra in the female

The so called "honeymoon pyelitis" and cystitis, common phenomena in early marriage, were supposedly brought about by sexual intercourse The same probably holds true among older married women who have intermittent episodes of cystitis It is interesting to observe that when the men were away during two World Wars the incidence of cystitis among their wives was much reduced

Pyelonephritis that exists in renal failure was said to be

common as compared with urinary tract infections in general. This was explained in two ways by Birchall and Alexander (10): either that most infections are limited to the lower urinary tract or that most infections represent actual invasion of the kidneys but that spontaneous or therapeutic cure is common.

Moffett and Goddard (11) reported pyelonephritis in 13.6 per cent of males with urethral strictures.

The clinical evidence presented indicates that pyelonephritis occurs in many conditions that result from local pathological changes and that it also is a frequent complication of certain generalized diseases.

Even more impressive are the facts provided by pathology concerning the frequency and seriousness of pyelonephritis. Perhaps the pathologists have done more than the clinicians to clarify the course of chronic pyelonephritis and to put it into proper perspective. A review of the literature on this subject confirms this.

In past years many diseases of the kidney had been diagnosed as glomerulonephritis. Weiss and Parker (5, 12) demonstrated that pyelonephritis was common in early childhood, in pregnancy, and again in old age. They pointed out the facts that chronic pyelonephritis might lead to arterial hypertension and to renal and cardiac insufficiency. Such late manifestations, they said, might take place when the original infection had subsided and healing had occurred. Furthermore, they stated that pyelonephritis was more often responsible for small contracted kidneys than was glomerulonephritis. They considered that chronic pyelonephritis was one form of Bright's disease. The classification of the various kinds of renal disease was becoming more clear.

Mansfield *et al.* (3) considered that chronic or healed pyelonephritis was an important type of Bright's disease. They classified chronic nephritis in three large groups:

1. Glomerulonephritis
   a. Subacute
   b. Chronic
2. Nephrosclerosis
   a. Benign
   b. Malignant

3 Pyelonephritis
a. Healed
b Chronic

Glomerulonephritis, they felt, should be restricted to lesions in which the primary change was a diffuse involvement of the glomeruli by an active or healed inflammatory process. In nephrosclerosis, the first and fundamental change was arterial, an arteriolar sclerosis. Healed pyelonephritis was said to be common as evidenced by old scarring of the kidneys at postmortem studies. In 1000 consecutive autopsies such scars were said to be present in 14 per cent of all persons. In their experience, the number of patients who had renal disease sufficient to lead to renal failure or to significant hypertension exceeded the number who had subacute or chronic glomerulonephritis. Glomerulonephritis, malignant nephrosclerosis and healed pyelonephritis ended in youth and early middle age, benign nephrosclerosis occurred after 50, and chronic pyelonephritis was found at all ages. That pyelonephritis was a common cause of Bright's disease was again demonstrated in finding that chronic pyelonephritis formed a larger group of patients with chronic Bright's disease than did glomerulonephritis (13).

Pyelonephritis was said to be the commonest lesion of the kidney found at autopsy by Allen (14) and in many instances the disease was marked. Nearly all adults at the time of death had microscopic foci of chronic pyelonephritis according to McManus (15) and often the disease was of considerable extent. At least 20 per cent of all patients coming to autopsy had gross or microscopic evidence of active or healed pyelonephritis according to Rhodes *et al* (16). It was significant that the condition was diagnosed before death in only 6 per cent of these patients.

Early in these studies, Butler and Lanman (17) reported that chronic pyelonephritis was the primary cause of death in approximately 2 per cent of 2013 autopsies on infants and children. Of these 63 per cent were under 2 years of age, 37 per cent were from 2 to 12 years of age, and 54 per cent of the infants and 79 per cent of the children had some anatomical malformation of the urinary tract.

In 32,360 autopsies studied by Bell (18), hydronephrosis was present in 1229 and 60 per cent showed pyelonephritis. Pyelonephritis was found present in 400 of 4425 autopsies by Jackson *et al.* (19), an incidence of 9 per cent. In 3 per cent of all autopsies pyelonephritis was found to be a chief contributing cause of death.

During the period of the discovery of the new antibiotics it seemed evident to these observers that, although some success had been obtained by their use, this was achieved chiefly in acute urinary infections. Among the patients who had recurrent or chronic infections failures were common. The number of patients who had chronic pyuria and bacilluria did not seem to have greatly diminished in spite of the newer therapeutic agents. Again, it was interesting that pyelonephritis was diagnosed at autopsy about five times as often as the clinical diagnosis had been made.

Acute pyelonephritis occurs in about 2 per cent of pregnant women (8) and has been said to occur in many pregnancies where there was physiological dilatation of the ureters.

That diabetics are more susceptible to infection than others has been well known. Pyelonephritis applies to such individuals in the same manner as other varieties of infection. Moreover, glycosuria may favor bacterial growth in the urine. At postmortem examination, evidence of kidney infection was found present in 20 per cent of diabetic women at the New England Deaconess Hospital in 100 autopsies by Barnard *et al.* (20). The same incidence of pyelonephritis in diabetics was reported by Joron *et al.* (21). They stated that pyelonephritis was a common postmortem finding in diabetics and that it often was not recognized during life.

Present and past literature from the clinician and the pathologist have shown that pyelonephritis in diabetics is high in incidence and serious in nature.

The incidence of pyelonephritis in our own experience is based upon a study of 1180 clinical records of patients at the Massachusetts General Hospital on whom a diagnosis of pyelonephritis was made. The years 1948 through 1956 are covered.

TABLE 1

Incidence of Pyelonephritis, Massachusetts General Hospital, 1948–1956

Year	No. of Cases	Hospital Admissions	Incidence %
1948	196	16,961	1.14
1949	103	17,063	0.60
1950	111	16,739	0.64
1951	165	20,799	0.70
1952	109	21,313	0.53
1953	149	21,407	0.60
1954	110	22,662	0.48
1955	120	22,679	0.51
1956	117	22,674	0.56
Total	1,180	182,297	0.6 approx.

The frequency with which pyelonephritis, acute or chronic, occurred in relation to total hospital admissions during these years is given in Table 1.

These figures indicate that during a 9-year period there has been no significant change in the incidence of pyelonephritis at this hospital. These years cover nearly a decade of active chemotherapeutic and antibiotic therapy.

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4

ETIOLOGY OF PYELONEPHRITIS

How bacteria reach the kidney in many instances of pyelonephritis is an important question that has not yet been adequately answered The three possible routes by which this may take place obviously are by the blood stream, through the lymphatics, or by direct ascent up the ureters Direct extension from nearby septic foci occurs, but has no place in this discussion.

Routes of Infection

In many cases of renal infection the route of renal invasion is clear, but how bacteria reach the kidney in patients who give no clear history of previous urinary tract infection and yet present themselves with advanced pyelonephritis is not yet clear There has been no satisfactory explanation of the method by which the kidneys become repeatedly infected in infancy and childhood, when no obstructive lesions can be detected and yet despite the continued administration of antibacterial drugs recurrent attacks of pyelonephritis persist In such cases it seems that the original renal infection never has been eliminated or that bacteria continue

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to reach the kidney from some other part of the body. The various theories concerning these problems, based on experimental evidence are presented.

Blood-borne Infections

Bacteria reach the kidney through the blood stream without doubt. Tubercle bacilli arrive in the kidney by the blood from some other focus, usually pulmonary, with the lymphatics as intermediary channels. Cortical renal infections are blood-borne from staphylococcal foci, often in the skin (1). In many other diseases it seems evident that renal lesions occur through the dissemination of organisms by the blood.

Many years ago Scott (2) reported an alarming incidence of positive blood cultures following urological procedures with a mortality of 18 per cent. The urethra was the probable portal of entry for these serious infections. The chills and fever that may *follow instrumentation of the urethra with positive blood cultures* obtained during the chill are positive evidence of bacteremia and indicate that organisms can reach the kidney by the blood stream (3)

An 88-year-old man came to the hospital with the chief complaint of "prostate trouble" For the past year he had had poor urinary control and dribbled most of the time

On examination, he was severely anemic with a Hgb. of less than 5.0 *mg* per cent caused by iron deficiency. The prostate was three times enlarged N.P.N., 86 mg per cent With multiple transfusions his Hgb rose to 14.0 mg. per cent and the N.P.N. fell to 52 mg. per cent The urine was sterile. About 18 hours after cystoscopic examination he had a shaking chill and his temperature rose to 102.2. The blood pressure dropped to 60/30. Urine, specific gravity, *1.006*–1.010; albumin, one plus; sediment, numerous W.B.C. Blood and urine cultures now grew *E. coli*. He was given intravenous chloromycetin and intramuscular streptomycin. In spite of treatment he died within 48 hours

At postmortem examination, beta hemolytic streptococci were cultured from the blood Acute and chronic pyelonephritis were prominent renal lesions (Fig. 8).

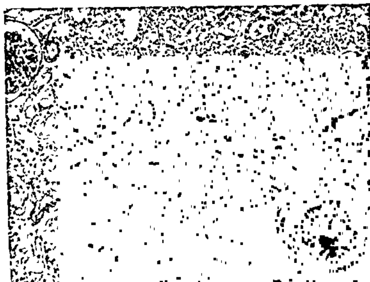


Fig 8 Acute focal pyelonephritis Hematogenous spread Death from septicemia Area of acute inflammation within and surrounding a group of tubules in the renal cortex Photomicrograph Low power

Clinical evidence, therefore, supports the theory that bacteria may reach the kidney by the blood in certain conditions

Experimental evidence also gives strong evidence that bacteria may reach the kidney by the blood stream and that this route may be important in the genesis of pyelonephritis

In 1932, Kennedy (4) produced renal lesions in rabbits by the intravenous injection of colon bacilli with and without ureteral obstruction The early lesions usually were in the region of the convoluted tubules or in the central portion of a papilla in the unobstructed kidney and in the cortex when there was ureteral obstruction In all types of experimental infection there was a rapid involvement of the entire kidney by a suppurative process.

These observations were followed by the experimental work of Mallory *et al* (5) Unilateral pyelonephritis was produced by injecting colon bacilli intravenously into rabbits after the partial

ligation of one ureter. Acute pyelonephritis, similar to that in man, was produced in the partially obstructed kidney in 75 per cent of the experimental animals. Extensive pyelonephritis was never found in the unobstructed kidney. Four to five days after releasing the ureteral obstruction following the intravenous injection of colon bacilli, the pyelonephritic process showed evidence of healing. Acute lesions were present as abscesses in the interstitial tissues. These arose around clumps of bacteria in the small blood vessels and from organisms that were present in the tubules. At the end of two months, the obstructed kidneys were markedly contracted to about one-half their original size and pale gray in color The histological lesions were similar, in most respects, to pyelonephritis in man. These authors considered that urinary obstruction was a very important factor in blood-borne pyelonephritis.

Further support for the blood stream as a method of renal infection was supplied by the experimental work of Beeson *et al.* (6). Small lesions produced by the electric cautery rendered an entire segment of the kidney susceptible to *E. coli* infection. The result was the same when the bacteria were introduced into the experimental animals by the blood stream or by way of the urinary bladder. It was believed that this susceptibility to infection in the damaged portion of the kidney was caused by renal tubular obstruction.

Ascending Infections

That renal infections may occur as a result of direct ascent up the ureteral lumen is a generally accepted fact (7–15). Attention was focused on this method by which pyelonephritis could take place by the frequency of this condition in infants and children who had obstructive lesions of the urinary organs.

Vesico-ureteral reflux had been demonstrated to occur by Graves and Davidoff in 1923 (16). Little attention was paid to this contribution until recent years when the problems associated with pyelonephritis became prominent. It is now appreciated that the reflux of urine to the kidney through the lumen of the ureter is a frequent cause of renal infection. Reflux occurs, at times, in

infancy and childhood when congenital abnormalities associated with obstruction to the free flow of urine are most frequent.

A 17-year-old boy came to the hospital with a history of pyelonephritis in infancy and malnutrition For years he had had abdominal pain, chills, and frequent urination His condition was poor. The left kidney was palpable and tender. N P N, 80 to 85 mg per cent, W B C, 16,500 Urine specific gravity, 1 000–1 012, albumin, three plus, sediment, many pus cells; culture, *E coli* Blood pressure, 115/60 Hgb, 65 mg per cent

A cystogram showed reflux up a dilated left ureter (Fig 9, A) Retrograde pyelography demonstrated marked left hydronephrosis and a vesical diverticulum (Fig 9, B) By retrograde pyelography the right kidney was small with clubbed calyces and a double ureter (Fig 9, C).

The right kidney was removed after a left nephrostomy was done The N P N rose to 125 mg per cent He died from *E coli* septicemia and chronic pyelonephritis

By delayed cystograms in children, Bunge (17) beautifully demonstrated vesico-ureteral reflux. He believed that reflux occurred only in disease and that in normal individuals reflux did not occur. Of considerable importance was the fact that, at times, upper urinary tract disease was detected by delayed cystography when intravenous pyelograms were considered to be normal

A 7-year-old boy had complained of attacks of chills and fever for a year Since birth there had been some difficulty in voiding Urine specific gravity, 1 021, albumin, 0, sediment, few W B C, culture, *Bacillus proteus* N P N, 27 mg per cent Blood pressure, 120/80 An intravenous urogram was not remarkable By a voiding cystogram, however, there was bilateral ureteral reflux, more marked on the right, with marked dilatation of the right ureter and renal pelvis (Fig 10) In spite of many antibiotics the infection persisted No obstructive lesion could be demonstrated.

The role that obstructive lesions play in the tendency to infection and the genesis of pyelonephritis already has been described. In this respect, diseases of the lower urinary tract are of

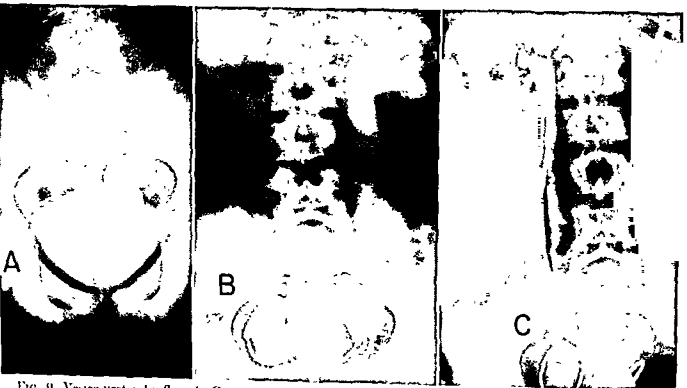


Fig. 9. *Vesico-ureteral reflux.* A. Cystogram with reflux up a dilated left ureter. B. Retrograde left pyelogram. Left hydronephrosis and small vesical diverticulum. C. Right retrograde pyelogram. Small right kidney with clubbed calyces and double ureter to upper half of duplicated kidney Catheter coiled in diverticulum



FIG 10 Vesico-ureteral reflux, more marked on the right, with dilated right ureter and renal pelvis Recurrent attacks of acute pyelonephritis

special significance. Narrowing of the urinary passages can be present from the vesical neck to the urethral meatus

A 75-year-old man had been operated upon four years before by transurethral surgery for a fibrous prostate Residual urines of 240

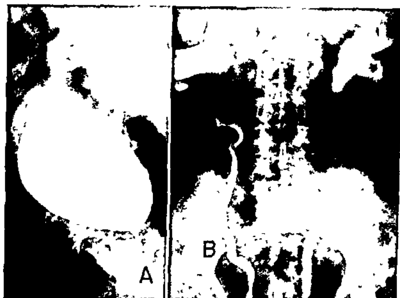


Fig. 11 A Cystogram. Post-prostatectomy. The bladder is atonic. B Bilateral retrograde pyelograms Both renal pelves are dilated. The ureters are tortuous and narrowed at their lower ends Chronic bilateral pyelonephritis

to 420 ml persisted after operation. The urine was infected, *E. coli* on culture Renal function was impaired: N P N., 66 mg per cent, P.S P, 20 per cent in two hours. Urine: specific gravity, 1.008, *albumin, 2 plus Hgb, 13 8 mg. per cent. Blood pressure, 170/90*

The bladder was atonic by cysto-urethrogram (Fig 11, A) and by cystogram. By retrograde pyelography, both kidney pelves were considerably dilated The ureters were tortuous and narrowed near *the bladder (Fig. 11, B). The renal infection could not be eliminated.*

Types of narrowing include urethral strictures, congenital or acquired, enlargements of the prostate, benign or malignant; calculous formation, vesical or urethral diverticula; neoplasms; inflammatory conditions, and disturbances of the central nervous system that affect normal vesical physiology. Any of these abnormal conditions may result in infection, reflux, pyelonephritis. Long ago, it was known that the first significant symptom of

prostatism was, at times, pain in the loin, chills and fever, and a sick patient. This was acute pyelonephritis caused by the reflux of infected residual urine to the kidney.

The high morbidity and mortality caused by spinal cord injuries have been well described in the past. Many of these patients died as a result of pyelonephritis, failing renal function, and uremia. This was brought to general attention by Prather (11) in paraplegic patients and by Bors and Comarr (18). Now, it should be standard practice to do cystograms and voiding cystograms on all patients who have enuresis, chronic pyuria, and many disorders of bladder function in an attempt to detect vesicoureteral reflux.

Lymphatic Extension

The facts that renal infections may result from a dissemination of bacteria to the kidney by the blood stream or by direct extension up the lumen of the ureter are well established. The evidence for extension of infection to the kidney directly by the lymphatics is not impressive. Certain early investigators firmly believed in lymphatic extension (19, 20). MacKenzie and Wallace (21), after a careful study of the problem, could find no evidence that infection from organs in the pelvis reached the kidneys by the lymphatics. However, it is quite possible that lymph channels from the pelvis can transport bacteria to the thoracic duct and that organisms can then reach the kidney by the blood stream.

Ascent by the Wall of the Ureter

In a recent convincing study, Talbot (22) has suggested another possible route by which infection in the bladder may reach the kidney. By observing the normal and abnormal physiology of the ureter, particularly in paraplegics, associated with vesico-ureteral reflux without mechanical obstruction, ureteral changes could best be accounted for by inflammatory processes in the wall of the ureter. This seemed to provide a reason for dilatation of the lower ureter gradually spreading upward toward the kidney and for the final irreversible changes from fibrosis. A continuous pathway exists in the subepithelial layer of the ureter to the renal

pelvis and to the interstitial tissue of the kidney by which organisms can spread from the bladder to the kidney. The inflammatory changes in the wall of the ureter interfere with normal peristaltic activity and stasis results. The susceptibility of the kidney to infection is increased by a functional obstruction of the ureter. Abnormal ureteral physiology was demonstrated by serial x-ray studies. The inflammatory reaction in the ureteral wall and within the kidney was evident in histological sections of ureter and kidney.

These observations of Talbot's are interesting in that they may explain the dilated and tortuous ureters that are present in instances of long-standing urinary tract infection. Here, also, is a fourth possible route by which infection may reach the kidney from the bladder.

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5

ACUTE PYELONEPHRITIS

Acute pyelonephritis has been regarded as the commonest disease of the kidney. Bacterial in origin, it is characterized by sudden onset, chills and fever, loin pain, dysuria, and, at times, hematuria Its presence often is unexplainable especially in uncomplicated cases, but predisposing factors are abnormalities of the urinary organs, obstructive lesions, calculous disease, and operative or instrumental procedures upon the urinary or other tracts. Incidence is highest in the early and late years of life and it is more common in females than in males. It is more prevalent in diabetes and in pregnancy than in normal states. Although most cases of acute pyelonephritis heal without appreciable damage to the kidney, its course in unpredictable and recurrences are common

Incidence

The number of admissions at the Massachusetts General Hospital of acute pyelonephritis from 1948 through 1956 is presented in Table 2. This is not at all representative of the actual incidence

TABLE 2

Incidence of Acute Pyelonephritis, Massachusetts General Hospital, 1948–1956

Year	No. of Cases	Cured	Not Cured	Died
1948	50	46	4	0
1949	39	34	5	0
1950	20	18	2	0
1951	47	45	2	0
1952	32	28	4	1
1953	33	32	1	1
1954	17	15	2	1
1955	22	19	3	1
1956	17	11	6	3
Totals	277 (0.15%)	248 (89.6%)	29 (10.4%)	7 (2.5%)

of this disease for a great number of such patients were successfully treated outside of the hospital.

These figures indicate that acute pyelonephritis is not as frequent in hospital admissions as chronic pyelonephritis. A high per cent of patients is cured and mortality is low.

The incidence of acute pyelonephritis was 0.15 per cent of hospital admissions to the Massachusetts General Hospital during the years 1948–1956, as contrasted with an incidence of approximately 0.6 per cent for chronic pyelonephritis.

Pathology

Acute pyelonephritis is an active infection particularly of the interstitial tissues of the kidney. One or both kidneys may be affected.

A man of 63 was brought to the emergency ward in coma. No adequate history was available and he was a diagnostic problem. Physical examination was unrewarding. His temperature was 101°. W.B.C., 16,000. Blood pressure, 115/80. He was oliguric. Urinalysis: sugar, 0, albumin, 2 plus, sediment, many W.B.C. and granular casts, pH, 5.0. N.P.N., 58 mg. per cent. Blood culture, no growth.



FIG 12 Acute pyelonephritis Death from septicemia. Both kidneys are swollen from intense acute inflammation Autopsy specimen.

Intensive antibacterial treatment was given but the N.P N gradually rose to 85, 115 and 128 He rapidly deteriorated and died in one week The diagnosis at autopsy was acute pyelonephritis and septicemia (Fig 12).

The diseased kidney is enlarged and, at times, considerably so (Fig. 12). The renal capsule may be thickened and somewhat adherent with small pin-point abscesses beneath its surface. On cut sections, the renal parenchyma is thickened and the normal markings are obscured Radial streaks extend from the cortex to the pelvis Multiple inflammatory areas are scattered throughout the interstitial tissues The renal pelvis and calyces may be of normal size or slightly dilated with the mucosa congested and perhaps covered with purulent exudate. The ureter often shows similar changes (1).

The microscopic appearance of acute pyelonephritis is one of

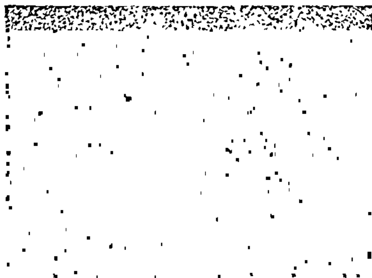


Fig. 13 Acute pyelonephritis Diffuse severe inflammatory reaction in the kidney with cellular infiltration composed of polymorphonuclear leukocytes Abscess formation The tubules are filled with cells and cellular debris The glomeruli are less involved Photomicrograph Low power

an acute suppuration. This process is a diffuse one with severe inflammatory changes interspersed with areas of normal parenchyma (Fig. 13) The epithelial lining of the pelvis and calyces is congested and edematous with leukocytic infiltration of the underlying connective tissue The medulla is similarly involved. The collecting tubules are surrounded by polymorphonuclear leukocytes and their tubular lumens are filled with cells and cellular debris The predominant inflammatory cells are neutrophils, but plasma cells, lymphocytes, and monocytes also are present The cortex shows similar changes Microscopic abscesses are in the cortex and in the medulla. The glomeruli are only diseased in the most serious degrees of inflammation when the glomerulitis described by Kimmelstiel and Wilson (2) occurs In the acute stage of the disease, degenerative vascular changes do not occur but fibrin formation in the walls of affected arterioles and small veins

may result in thromboses. In most instances of acute pyelonephritis healing is complete and renal function returns to normal although focal scar formation may occur.

Symptoms

The onset of the disease is sudden and patients with acute pyelonephritis are really sick. The characteristic symptoms are shaking chills, a high temperature, costovertebral tenderness, and frequent and painful urination. At times, symptoms are severe, particularly when the blood stream is invaded. Usually, however, the disease is of short duration, particularly in uncomplicated cases with present therapy. Occasionally, lower abdominal pain is an early symptom, especially in women, and an intra-abdominal lesion may be suspected. Sudden, severe lumbar pain with acute pyelonephritis has been the first symptom of prostatism, caused, I believe, by vesico-ureteral reflux.

In infancy and early childhood, the early symptoms of acute pyelonephritis may be difficult to evaluate since pain, sometimes abdominal, is difficult to localize and the presenting symptoms often are nausea and vomiting and a sick child.

The severest forms of acute pyelonephritis occur in sudden blockage of a kidney associated with prostatism and in diabetics where there is necrosis of the renal papillae with extensive renal damage. This is discussed again under pyelonephritis in diabetics.

A man of 68 was admitted to the hospital because of urinary retention and left flank pain. He was dehydrated, acutely sick with chills and fever The left kidney was tender. The prostate was moderately enlarged Blood pressure, 140/80 Urine: specific gravity, 1 016; albumin, 1 plus, sugar, 0; sediment, R. and W.B C.; culture, alpha hemolytic streptococci W.B C., 20,000.

Blood chemistries: N.P.N., 44 mg per cent; Na, 133; K, 4 9, Cl, 90, CO_2, 31. *Fasting blood sugar, 161.*

The right kidney was normal by intravenous pyelography but the left kidney was only faintly visualized *His pain was relieved by* passing a catheter to the left kidney. Urine from this kidney was full of pus cells and streptococci were cultured. A retrograde left pyelogram showed an irregularly dilated ureter and a ragged renal pel-

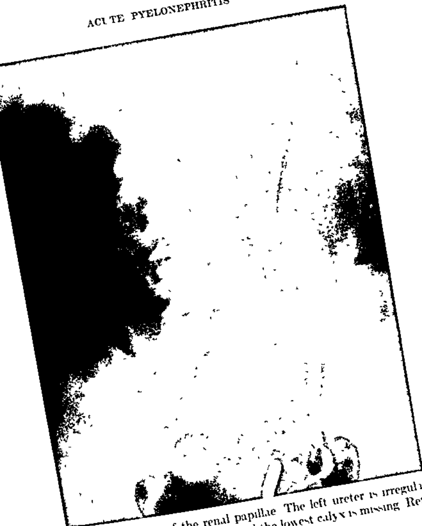


FIG 14 Necrosis of the renal papillae The left ureter is irregularly dilated The renal pelvis is ragged and the lowest calyx is missing Retrograde pyelogram

vis with the lowest calyx missing (Fig 14) The N P N dropped to 32 mg per cent

With intensive antibacterial treatment he completely recovered from severe acute pyelonephritis and necrosis of the renal papillae (Fig 15)

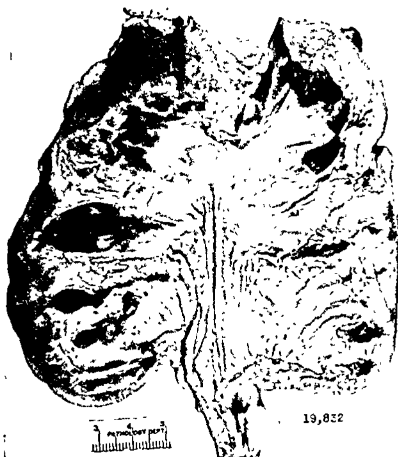


Fig. 15 Necrosis of the renal papillae A man of 74 with prostatic obstruction Death from severe sepsis. The left kidney is severely damaged with necrosis of all the renal papillae Autopsy specimen

Diagnosis

The typical symptoms of chills, fever, loin ache, and urinary symptoms suggest the diagnosis of acute pyelonephritis When these are accompanied by pyuria the diagnosis is apparent. At times, however, the urine is clear while the temperature is rising and pus cells appear only later when the suppurative process in

the kidney communicates with the excretory apparatus In other words, the urine is normal when only the interstitial tissue of the kidney is infected and the renal tubules are not yet involved During this stage of the disease urine cultures may be positive in the absence of pyuria (3).

Early in an attack of acute pyelonephritis fever, leukocytosis and abdominal tenderness may simulate an intra-abdominal process such as acute appendicitis The absence of significant urinary findings at this time may lead to errors in diagnosis

Examination of the urine usually shows important changes that help in diagnosis Albumin is present in varying amounts Bacteria will be found by culture or in the stained sediment at some time during the course of the infection The gram stain will tell whether the organisms are cocci or bacilli and this will be an aid in determining the best immediate treatment Cultures of freshly procured urine will identify the bacteria and give their sensitivity to antibacterial agents

Quantitative bacterial counts have been advocated as a method of determining the presence of active urinary tract infection Marple (4) advocated the agar pour-plate technic for quantitative bacterial counts. This was emphasized by Sanford *et al* (5) who felt that bacteriuria of approximately 1000 viable organisms per ml was necessary for a diagnosis of infection and that the presence of a moderate number of bacteria by stained smear was suggestive of significant bacteriuria

A thorough study of this problem was made by Kass (6) It was his opinion that even a few bacteria from the kidney could lead to the presence of a great many bacteria in the bladder urine Urine from the renal pelvis of patients with kidney infections was said to have contained as few as 10,000 bacteria per ml while, at the same time, the bladder urine contained more than 10^5 organisms per ml True bacilluria probably existed when the bacterial counts were 10^5 or more per ml of urine Counts lower than this were considered probable contamination

Most writers agree that the quantitative estimation of bacterial population in the urine is subject to many variables These are dilution pH of the urine, the stage of the renal disease, the

presence of obstructive lesions, the brand of infecting organism, and whether antibacterial drugs have been administered. It is important that urine specimens be carefully obtained and promptly processed Close cooperation with the bacteriologist will pay dividends.

Methods of collecting urine for study have been the subject of considerable debate. This applies particularly to the use of the catheter to obtain specimens. The usually accepted methods have been a clean-voided specimen in the male. This means a cleansing of the glans and meatus and urine collected in a sterile container after some urine has been passed to wash out organisms from the distal urethra. These simple precautions are necessary since it is well known that in the male the meatus and nearby skin are heavily populated Bacteria have been reported present at a depth of 5 cm. in the normal male urethra (7). Such studies have varied and it has been uncertain that the bacteria present were in fact pathogenic In this respect, quantitative tests would seem to be important. Unnecessary catheterization of the male, I believe, is generally recognized. The clean, voided specimen usually is a reasonably reliable method for the collection of urine specimens from the male.

With the female, the situation is different. The normal female urethra harbors bacteria In 50 per cent of 114 normal pregnant women, bacteria were found to be present in the urethra (8). Since this is so, it has been suggested that the use of the catheter may drive organisms into the bladder. This undoubtedly is true but it is difficult to infect the normal bladder even by the introduction of pathogenic organisms The abnormal bladder often is infected, or readily becomes so, but the use of a catheter usually is necessary in such cases. Cystitis may result, but it is not apparent how often cystitis leads to pyelonephritis. Voiding specimens of urine in women have been suggested (9), but they all seem complicated and their technic undignified. With care and sterile precautions, catheterization is a reasonably safe method for collecting urine specimens in the female.

Prophylactic chemotherapy may have a place in the prevention

of infection following catheterization or instrumentation When an inlying catheter is present, however, prophylactic chemotherapy only eliminates organisms that are susceptible to treatment and favors the establishment of resistant strains Prophylactic treatment with sulfonamides was said to be a failure in preventing urinary infections after vaginal operations. Infections occurred as often in treated patients as in those who received no prophylactic treatment. When prophylaxis was given, *Streptococcus fecalis* infections were said to be likely to occur (10)

Roentgen Examination

X-ray examination is necessary in all cases of acute pyelonephritis. Plain films give an estimation of the size and position of the kidneys and the presence or absence of calculi Intravenous injection of one of the organic iodine preparations provides valuable *information regarding renal function, abnormalities of* size and position and, of particular importance, the presence of obstructive lesions that predispose to infection

In acute uncomplicated pyelonephritis, intravenous urography usually shows no abnormalities Retrograde studies are indicated only when the diagnosis is obscure Renal function is little, if any, disturbed in spite of the diffuse involvement of the kidney by the infectious process. The renal pelvis and calyces are sharply outlined and usually appear normal At most, there may be slight dilatation of these structures but there are no gross abnormalities of significance (Fig. 16). In infancy and childhood, roentgen examination is of the greatest importance since congenital urinary tract abnormalities are common and are responsible for many of the instances of acute infection. This is true also in pregnancy and diabetes

Treatment

Acute pyelonephritis, uncomplicated, almost always responds well to modern treatment Certain complicated infections may respond to treatment (Figs. 17, 18, 19)

Effective therapy is based upon identification of the infecting



FIG 16 Acute pyelonephritis. A woman of 44 with acute *E. coli* pyelonephritis. Retrograde pyelograms were made for good reasons although they are seldom indicated in acute renal infections. The right renal pelvis is a little dilated and the upper left calyx is irregular from acute inflammation

organism and its susceptibility to the many available antibacterial agents that we now have. This is the basis of intelligent therapy.

How patients with acute pyelonephritis fared in our hands is



FIG 17 Acute pyelonephritis and carcinoma of the cervix A Postoperative intravenous pyelogram Considerable dilatation of right renal pelvis Pyuria with *E. coli* in urine B One month later. The hydronephrosis has disappeared Both kidneys normal Urine sterile after appropriate antibacterial treatment

presented in Table 3. The results of treatment, even in cases complicated by obstructive lesions, calculi, etc., have been good and mortality has been low. Most of the deaths occurred when virulent organisms resistant to antibacterial treatment were present.

Prognosis

Many instances of acute pyelonephritis respond well to adequate doses of the sulfonamides but a good response does not necessarily mean a complete cure The serious results of inadequate treatment of the initial attack of renal infection cannot be overemphasized. Here is the one chance of preventing re-



FIG. 18. Acute pyelonephritis and lymphatic leukemia. Both kidneys are infiltrated with this disease. Superimposed acute renal infection, *E. coli* and *B. proteus*. The acute infection was cured by appropriate medical treatment. Intravenous pyelogram.

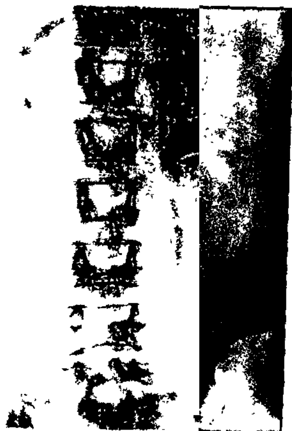


FIG 19 Acute pyelonephritis and lymphoma A woman of 38 with severe acute left renal infection, *E coli* and nonhemolytic streptococci in urine. Left nephrectomy Intravenous pyelogram

curring similar episodes and preserving renal function Treatment should be continued not only until the patient is symptom free and the urine is normal but until repeated urine cultures are bacteria free With every precaution taken, however, repeated episodes of acute infection may take place either because the initial infection has never been completely eliminated or because

TABLE 3

Results of Treatment, Massachusetts General Hospital, 1948-1950

	No of Cases	Cured	Not Cured	Died
Uncomplicated	196	181 (92.4%)	15 (7.6%)	5 (2 5%)
Complicated	81	67 (82.7%)	14 (17.3%)	2 (2.4%)
Total	277	248 (89.6%)	29 (10 4%)	7 (2 5%)

TABLE 4

Bacteriology, Massachusetts General Hospital, 1948-1950

	No of Cases	Per Cent (Approx)
E coli	177	63 5
Staphylococci	17	6.1
Streptococci	9	3 3
B pyocyaneus	2	0 7
B. proteus	9	3.2
Mixed infections	49	17.7
No growth	13	4.5
Not cultured	1	0.3
Total	277	100.0

the kidney continues to receive pathogenic organisms from some focus.

In early uncomplicated acute pyelonephritis E. coli is the usual responsible organism In 277 cases of acute pyelonephritis at the Massachusetts General Hospital, *E coli* was the only organism cultured in 176 or 63.5 per cent of the cases (Table 4). In complicated cases or where there have been repeated episodes of infection other bacteria such as *B. proteus*, *Bacillus pyocyaneus* and enterococci often are present.

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6

TREATMENT OF URINARY TRACT INFECTIONS

Chemotherapy and the Antibiotics

The past history of the treatment of urinary tract infections is interesting. Years ago, treatment attempted to modify or to eliminate bacteria by forcing fluids and changing the urinary pH. A pH of less than 5.0 was necessary to have a bactericidal effect on most bacteria. Extreme dilution of the urine was found to hinder only slightly bacterial multiplication. These methods had only a limited success.

Hexamethylenetetramine (methenamine, Urotropin) once was a common remedy for urinary infections. This compound in an acid medium breaks down to liberate formaldehyde as a bactericidal agent. Sodium acid phosphate was added to acidify the urine. The success of this therapy was limited and it often caused irritation. Hexylresorcinol (Caprokol) was used on the theory that it reduced the surface tension of the urine. Pyridium followed in 1926 and Serenium in 1930 as urinary antiseptics. Vaccines were given a

trial and discarded as was bacteriophage None of these methods was very effective in destroying invading organisms Many patients recovered without treatment

Ketogenic Diet

Real progress was made in the treatment of these infections by the discovery that beta-hydroxybutyric acid inhibited bacterial growth in an acid urine This was the basis of the ketogenic diet (1, 2) Although the ketogenic diet presented patients with a rugged routine, it was more effective than former methods in eliminating bacteria from the urine, especially *E coli*

Mandelic Acid

A derivative of beta-hydroxybutyric acid, mandelic acid in various forms, a natural sequel to the ketogenic diet, was effective in many infections caused by *E coli* and *S fecalis*, It was ineffective against staphylococci and urea splitting bacteria such as *B proteus* Mandelic acid soon took the place of the ketogenic diet. The success of mandelic acid therapy depended upon maintaining the pH of the urine at less than 5 5 (3), so acidifying agents such as ammonium chloride were added A convenient preparation was a combination of mandelic acid and methenamine, called Mandelamine Dose 1 0 gm four times a day Fluids were restricted to 000 ml in 24 hours If renal function was normal, this treatment used no renal damage Its advantages were ease of administration on lack of toxic reactions, and effectiveness against several types organisms (4) Mandelamine still is useful, especially in uncomcated urinary infections caused by *E coli*

fonamides

he first of these drugs was introduced in 1933 as Prontosil (5) ntosil was bactericidal to streptococci Sulfanilamide, one of its atives, was excreted in the urine in sufficient amounts to be ricidal More effective than mandelic acid, the sulfa drugs d a new era in chemotherapy It was soon appreciated that drugs could be severely toxic Sulfanilamide has been said to

be as effective as its derivatives in the treatment of uncomplicated *E. coli* infections The later modifications, however, are said to have a broader range of action with respect to other organisms and to be less toxic than sulfanilamide (6).

Sulfapyridine

This agent was found to have no place in urinary infections because the precipitation of the insoluble acetyl form of the drug caused blockage of the renal tubules. Hematuria occurred in about 25 per cent of patients given this drug. Sulfapyridine proved to be the most toxic of the sulfa drugs.

Sulfathiazole

This was introduced in 1940 and was found to be superior to sulfanilamide and to be effective in small doses This drug, however, required a high fluid intake since the nonsoluble acetyl sulfathiazole also could cause blockage of the renal tubules. Sulfathiazole was rapidly absorbed and quickly excreted by the kidney. It was effective in many types of infections, especially those caused by staphylococci and *S. fecalis.*

Sulfadiazine

This preparation gave a higher concentration in the blood than sulfathiazole and was less toxic than any of the previous sulfonamides. Effective blood levels were reached within two to four hours and 90 per cent of the drug was eliminated by the kidneys Sulfadiazine was said to be effective in infections caused by *E coli*, streptococci, pneumococci, and the Friedlander's bacillus.

Subsequent modifications of the sulfa drugs have been too numerous to mention With all the competition these drugs have had in recent years they still hold a place in the treatment of urinary infections Their advantages are reasonable safety, although patients may become sensitive to their use and continued treatment may have to be stopped, ease of administration, and the effectiveness of these drugs against many different invading bacteria. If they are used, the most soluble preparations and those of low toxicity should be prescribed In acute uncomplicated infections

it is reasonable to give these drugs in adequate doses until the patient has been studied and until the infecting organisms have been identified and sensitivity tests have been reported Since acute uncomplicated pyelonephritis most often is caused by *E coli*, the sulfonamides usually will be effective

Sulfonamide Combinations

Combinations of the sulfonamides have been said to have certain virtues not possessed by a single drug. Schweinberg and Rutenburg (6), however, concluded that sulfonamide mixtures were justified only when *in vitro* sensitivity tests demonstrated an additive or potentiating effect for the components of the mixture Tests suggested that this was likely to be true for coccal infections but not for gram-negative infections

Sulfamethoxypyridazine (Kynex)

Prolonged treatment for cases of chronic pyelonephritis has been advocated because from the course and pathology of this disease long courses of treatment seem reasonable In spite of all the available antibacterial drugs, experience has shown that many patients become refractory to treatment This recently available sulfonamide may provide a suitable drug for long-term chemotherapy The antibacterial activity of sulfamethoxypyridazine is comparable to that of sulfadiazine It is readily absorbed from the gastrointestinal tract and is slowly excreted into the urine Freedom from crystalluria and the absence of a significant accumulation of the drug in the usual doses, even in azotemia, are said to be assets in prolonged therapy Toxic reactions are similar to those produced by other sulfonamides This agent is most effective in *E coli* infections, with other organisms or mixed infections the results of treatment have not been as good Susceptible bacterial strains have been eliminated after one or two weeks of treatment or not at all (7)

A distinct advantage of sulfamethoxypyridazine is that an initial dose of 1 0 gm followed by 0 5 gm every 24 hours provided adequate concentrations in the blood of most patients and the single daily dose is said to be more potent than sulfisoxazole (Gantrisin)

and sulfadimitine (Elkosin) in experimental infections in animals. Of particular interest has been the possibility of preventing, by its use, pyelonephritis in pregnancy and in the puerperium in women with persistent bacilluria. It is believed this long-acting antibacterial drug, with its smaller and less frequent doses than others, may be useful (8).

Penicillin

This is a mold discovered by Fleming (9) in 1929 but it was not used as an antibacterial agent until 1941 when such agents were sorely needed during World War II. It was then found that this antibiotic was highly effective against coccal infections (10). Effective as penicillin proved to be, it was soon recognized that staphylococci became increasingly resistant to its use. At the present time, susceptible strains of these organisms number only a relatively small per cent. Of 448 strains of *Staphylococcus aureus* isolated from wound infections tested at the Massachusetts General Hospital in 1957, only 38 per cent were penicillin sensitive. Resistant strains were present chiefly among hospital patients, whereas in patients who had had no hospital admissions the staphylococci were more likely to be sensitive to penicillin. Enterococcal urinary tract infections usually have responded well to penicillin.

Streptomycin

Derived from a streptomyces, this antibiotic was introduced in 1945. After intramuscular injection, streptomycin appears in the urine within one hour and 65 per cent is excreted in the urine within 12 hours. Its concentration in renal tissue is said to be twice that in the blood. *The activity of streptomycin increases five to ten times with each unit increase in the pH of the urine, so alkalies should be given during treatment to keep the urinary pH as near pH 8.0 as possible.*

Although streptomycin is very effective against many gram-negative bacteria, its effectiveness is impaired by the frequency and rapidity with which bacteria become streptomycin resistant. It usually loses its effectiveness after about five days of treatment

(11) Resistance is very rapidly acquired when catheters c are present and streptomycin then is ineffective

Toxic manifestations of streptomycin are damage to the ular apparatus and severe skin reactions Dihydrostrepto usually is used only when patients are sensitive to strepto and it is more likely to produce deafness than streptomycin average dose of streptomycin is 1 0 gm daily in a single intra cular injection Sodium citrate, 4 cc of a 50 per cent solution given by mouth three to four times a day

Chloramphenicol (Chloromycetin)

This was one of the first reported broad-spectrum antibiotics About 10 per cent of the ingested amount of this drug is excreted in the urine Chloramphenicol is effective against gram-positive and gram-negative bacteria and has been of great value in the treatment of urinary tract infections Staphylococci are said to develop resistance slowly to this antibiotic, *E coli* becomes resistant more rapidly Some strains of *B proteus* are sensitive to chloramphenicol It is not effective against *Pseudomonas aeruginosa.*

The usual dose of chloramphenicol is mg 250 to mg 500 four times daily Hematological complications following the use of this antibiotic have been overemphasized and there should be no hesitation in prescribing it for severe infections or those resistant to other agents if the infecting organism is sensitive to chloramphenicol This drug may be given intravenously or intramuscularly

Tetracyclines

There are three antibiotics in this group Chlortetracycline (Aureomycin) was discovered in 1948 Oxytetracycline (Terramycin) was available in 1950 Tetracycline (Achromycin, Panmycin, Polycycline, Steclin, Tetracyn) was brought out in 1953 The chemical formulas of these three compounds are similar These antibiotics are primarily bacteriostatic for both gram-positive and gram-negative bacteria Sensitive organisms are said to develop resistance slowly to these drugs Although there is a general similarity in bacterial spectrums covered by these three drugs, there is

said to be a variation in the sensitivity of different strains of the same species of bacteria These drugs diffuse into all body fluids and tissues and are excreted in the urine. Ten to 20 per cent of the amount ingested is excreted in the urine in the first 12 hours

Urinary tract infections caused by susceptible bacteria usually respond well to treatment with the tetracyclines but relapses after treatment have been high. Ease of administration and relative effectiveness have led to a widespread use of these drugs in the treatment of urinary tract infections (12).

The tetracycline group of drugs is especially effective against infections caused by *E. coli*, *Aerobacter aerogenes*, staphylococci and enterococci. Oxytetracycline (Terramycin) is more effective than the other against *P. aeruginosa*. Tetracycline (Achromycin) is most effective against *Proteus mirabilis*. In surgical infections, these drugs are effective in most cases caused by *E. coli* and *A. aerogenes* but they are of very limited value in infections caused by *B. proteus* and Pseudomonas. Staphylococci have become increasingly resistant to the tetracyclines.

A disadvantage of this group of antibiotics has been their tendency to cause gastrointestinal disturbances. Severe or fatal staphylococcal lesions of the intestinal tract have been reported following their use. In this respect, oxytetracycline (Terramycin) is said to be accountable for such trouble in about 30 per cent, chlortetracycline (Aureomycin) in approximately 20 per cent, and tetracycline (Achromycin) in only 5 per cent of cases.

The customary dose for adults of the tetracyclines is 1.0 gm. daily divided into four doses. Capsules of mg. 250 each are taken by mouth. Sterile powder is available for intravenous use but due care should be taken not to give the drugs too fast or in too concentrated solutions since this may lead to a chemical phlebitis Intramuscular injection is painful and rectal administration is useless.

Erythromycin

Deprived from a streptomyces, this antibiotic, like penicillin, is useful chiefly in staphylococcal and enterococcal infections of the urinary tract. Bacteria may become resistant to this drug

with great rapidity in spite of initial susceptibility. It has been of considerable value in the treatment of penicillin-resistant strains Toxic effects are not common and are mostly gastrointestinal in nature The dose and administration are similar to those of the tetracyclines

Carbomycin

This drug is similar in activity to erythromycin but is less effective and has no advantage over erythromycin

Novobiocin (Albamycin, Cathomycin)

This antibiotic is also derived from a streptomyces Higher blood levels are said to be reached with novobiocin than with other antibiotics because of slower urinary excretion It is useful chiefly in coccal infections of the urinary tract and against organisms resistant to penicillin and erythromycin Rashes and urticaria are about the only side reactions from its use and these occur in 10 per cent of patients Bacteria quickly become resistant to novobiocin so treatment usually is continued for only five days Dosage and administration are similar to erythromycin (13), although 500 mg by mouth (2 capsules) every 6 hours has been recommended in the treatment of moderately severe infections in adults This drug may be given intravenously in 500-mg doses at 12-hour intervals and intramuscularly in 250-mg. amounts every 6 or 8 hours (14)

Cycloserine (Seromycin)

This drug has been used chiefly in the treatment of tuberculosis but all common bacteria have been said to be sensitive except Pseudomonas, *B proteus* and *S fecalis* It has been reported to be useful in small doses in the treatment of chronic infections in women over long periods of time Toxic reactions occur with large doses so 500 mg or less each day is advised (13)

Neomycin

This is an antibiotic derived from a strain of streptomyces in 1949 *In vitro* it is bactericidal to a large variety of both gram-

positive and gram-negative organisms. It was hoped that this agent could be used in *B. proteus* infections since it did have a favorable effect against these stubborn bacteria and there was little tendency for the organisms to become resistant. The dose advised is 0.5 gm. dissolved in 2 ml. of sterile physiological saline solution given intramuscularly four times a day.

Although Neomycin is highly effective against *E. coli*, *A. aerogenes*, *S. aureus* and *P. aeruginosa*, unfortunately it has serious toxic effects. Because of toxicity to the ear and the kidney, Neomycin is used only in desperate situations. One gram daily is said to be safer than doses of 2.0 gm. (15).

Kanamycin

Recently discovered by the Japanese, this antibiotic is said to be predominantly bactericidal. It is similar in structure and activity to neomycin. Kanamycin is particularly active against the *staphylococcus*, *E. coli* and the aerobacters and has variable activity against *B. proteus* and pneumococci. Major toxic effects are on the kidney and on the eighth nerve. If used with caution because of its toxicity, kanamycin should be useful in the treatment of difficult staphylococcal urinary tract infections. Doses of 0.5 to 2.0 gm. daily in adults and 15 to 50 mg. per kg. of body weight a day in infants have been advised, given as 2 to 4 doses every 6 to 12 hours (16).

Polymyxin B

Polymyxin is a generic name for antibiotics elaborated in the fermentation of various media by strains of *Bacillus polymyxa*, a spore-forming bacillus found in soil (17). This antibiotic is primarily active against gram-negative bacteria especially *E. coli* and *P. aeruginosa*. It is not useful in infections caused by *B. proteus* or hemolytic streptococci. It is one of the few agents effective against *P. aeruginosa*. The recommended dose is 2.5 mg. per kg. of body weight divided into 4 doses given intramuscularly every 6 hours. The drug should have 25 mg. to 50 mg. of 1 *per cent* procaine added to lessen the pain of the injections.

Neurotoxic symptoms almost invariably occur when polymyxin

is given. These are paresthesias and hypesthesias about the face and scalp, mild dizziness and weakness. These symptoms are said to disappear within 24 hours. Some effect on the kidney has been reported but there has been no permanent damage known to man (18, 19).

Bacitracin

This is an antibiotic derived in 1943 from an aerobic gram-positive spore-forming bacillus. First used locally in surgical infections caused by gram-positive bacteria with good results, it was later applied to urinary tract infections. It is effective only against the staphylococcus. Since bacitracin has toxic effects upon the kidney it should be used only when other drugs are ineffective. This is because of its toxicity. Skin rashes were said to occur in 15 per cent of cases, nausea and vomiting in 25 per cent, albuminuria in 25 per cent. Local pain from injections was present in 35 per cent. The usual dose of bacitracin has been 20,000 to 65,000 units intramuscularly every 6 hours. This drug is only used when other agents are ineffective (20, 21).

Nitrofurantoin (Furadantin)

This is one of the nitrofurans and the first of the group designed for systemic administration. Furadantin is produced synthetically and is not an antibiotic. About 40 per cent of the oral dose is excreted in the urine, the major portion within 4 hours after ingestion. After 8 hours the urine is practically free of the drug (22). It is said to be effective against the majority of strains of *E. coli*, *B. proteus*, *A. aerogenes*, *S. fecalis* and Alkaligenes but ineffective against *P. aeruginosa*. It is more useful in acute than in chronic urinary tract infections.

Toxic effects from Furadantin are few, mild gastrointestinal upsets being the main symptoms. The usual dose is 100 mg. by mouth four times a day (23).

Vancomycin (Vancocin)

This recent antibiotic is said to be useful in staphylococcal infections especially in septicemia. The drug is not absorbed when

given by mouth and is irritating when it is given intramuscularly. It is administered intravenously in doses of 2.0 gm. daily.

Combinations of Antibiotics

A comprehensive study of the effectiveness of antibiotic combinations was made by Jones and Finland (24). They felt that such combinations encourage inadequate treatment because there is a tendency to use the same total dose of the combination as of the single agent so that the effective dose of either drug is not given. Advocating the use of the antibiotic combinations studied could not be justified by their data and was considered to be bad practice

Dowling (25) concluded that the administration of combinations of antibiotics was indicated only in a few highly selected conditions and that they have been advocated in other conditions in which they not only do no good but actually may be harmful. When combined therapy is indicated, the antibiotics should be given separately.

The changing pattern of pathogenic bacteria to antibacterial agents is illustrated in the tabulations compiled by Dr. L. J. Kunz and Dr M. Swartz of the bacteriology department of the Massachusetts General Hospital.

During a three-year period, penicillin and streptomycin had gained in their effectiveness against the staphylococcus (Table 5) The tetracyclines, on the other hand, had lost ground in this respect Chloromycetin and erythromycin had held their own in effectiveness. The effectiveness of penicillin was temporary, for shortly after this report less than 40 per cent of the staphylococcal strains were sensitive to penicillin. Bacitracin was seldom used.

As reported in Table 6, the tetracyclines again seemed to be losing their effectiveness in all types of urinary infections. Bacteria appeared to have become more resistant to Furadantin especially in infections caused by *E. coli* and *B. proteus* where it had been most effective. Chloromycetin retained its place as an effective agent in most of these infections, especially those caused by *B. proteus* and *E. coli*. In spite of their toxicity, polymyxin and

TABLE 5

Sensitivities of Pathogenic Bacteria (Staphylococci) to Antibiotics, Massachusetts General Hospital

Antibiotic	April–June 1954 Per Cent Sensitive	April–June 1957 Per Cent Sensitive
Penicillin	29	68
Streptomycin	59	79
Terramycin	68	56
Aureomycin	75	63
Achromycin	69	59
Chloromycetin	98	97
Erythromycin	97	97
Bacitracin	—	99

TABLE 6

Urinary Tract Pathogens, Massachusetts General Hospital

Antibiotic	April June 1954 Per Cent Sensitive			April June 1957 Per Cent Sensitive		
	E coli	*B proteus*	*B pyocyaneus*	*E coli*	*B proteus*	*B pyocyaneus*
Streptomycin	38	48	2	53	58	18
Terramycin	64	18	6	38	1	0
Aureomycin	57	18	10	26	3	0
Achromycin	67	16	20	39	4	3
Chloromycetin	82	59	40	79	82	22
Furadantin	83	85	7	66	59	18
Polymyxin	—	3	58	—	—	75
Neomycin	91	100	64	99	98	75

Neomycin appeared to be most effective in the worst types of urinary infections

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7

CHRONIC PYELONEPHRITIS

One of the most serious afflictions of the kidney is caused by the long indolent course of chronic pyelonephritis. Bacterial in origin, many years often elapse before smoldering infection destroys so many functioning renal elements that the kidney no longer is able to perform its many tasks efficiently. The final outcome is uremia and death. The pathological changes are characteristic. Symptoms often are vague and misleading. Diagnosis may be difficult. Treatment is unsatisfactory. Prognosis is uncertain. Many of the facts concerning this disease are discussed in Chapter 1.

A laborer of 37 came to the hospital because of weakness and loss of strength. His N.P.N. was 58 mg. per cent and his blood pressure was 158/92. Urine: specific gravity, 1.010–1.012; albumin, 4 plus, sediment, a few R.B.C. and W.B.C.; culture, *S. albus* By intravenous urography there was no visible right kidney function and the left kidney was poorly visualized A retrograde right pyelogram showed a small shrunken kidney (Fig 20).

He did poorly on medical treatment and was readmitted ten



FIG. 20 Chronic pyelonephritis A man of 37 with severe bilateral renal disease The right kidney is small and the calyces are dilated The pelvis and calyces of the larger left kidney also are irregularly dilated N P N, 260 mg per cent Blood pressure, 160, 100 Death in uremia in 2 years Retrograde pyelograms



FIG 21. Chronic pyelonephritis, severe, bilateral. Death in uremia Chronic inflammation with widespread scarring, extensive glomerular hyalinization, tubular destruction and arterial thickening. Sparse inflammatory infiltrate. Photomicrograph. Low power.

months later. At this time his N P.N. was 74 mg per cent He was nauseated and was vomiting. The blood pressure was 160/100 and there was marked retinopathy. Hgb., 10.2 gm The N.P.N. gradually rose to 260 mg per cent; CO_2, 13 7. His heart was enlarged The blood pressure rose to 180/120

Within ten days he died in uremia from chronic pyelonephritis (Fig 21)

Pathology

The gross renal changes of long-standing chronic pyelonephritis are kidneys that are pale and shrunken. Kidney size may be reduced to one-third of normal. Although the disease commonly involves both kidneys, it may be more advanced on one side (Fig 22). Atrophy may be so great that congenital hypoplasia is sus-



Fig. 22 Chronic pyelonephritis with atrophic right kidney A woman of 22 with *E. coli* urinary tract infection The right kidney is small (weight, 25 gm) The left kidney is hypertrophied Right nephrectomy Retrograde pyelograms

pected Differentiation between these two conditions is not always simple (1) (Fig 23)

Grossly the renal capsule is white and firm and strips away with some difficulty The external surface of the kidney itself is scarred and irregular with shallow or deep depressions. Normal tissue forms lobular bulges between scarred areas (Fig 24)



FIG 23 Renal hypoplasia and chronic pyelonephritis Recurrent attacks of chills and fever Urine infected with *E. coli*. The left kidney is undeveloped The ureter is dilated. Left retrograde pyelogram Left nephro-ureterectomy.



FIG 21. Chronic pyelonephritis Both kidneys are shrunken with scarred irregular surfaces A man of 31 Hypertension for 4 years, blood pressure, 240/140 Narrowed renal arteries Death in uremia Autopsy specimen

Cut sections of the diseased kidney show varying changes depending upon the extent of renal involvement The relative amounts of cortex and medulla may not be changed but in advanced disease the cortex is diminished in size and the medulla is more prominent. Scattered throughout the parenchyma are pale, whitish striations that represent areas of fibrous tissue The pelvis and calyces may be normal or dilated with thickened, fibrotic walls The ureter is either of normal size or dilated and tortuous from inflammatory reaction and fibrosis (2)

Microscopically, the histological abnormalities are those of chronic inflammation When there is active infection, polymorphonuclear leukocytes are present in the tubules and in the interstitial

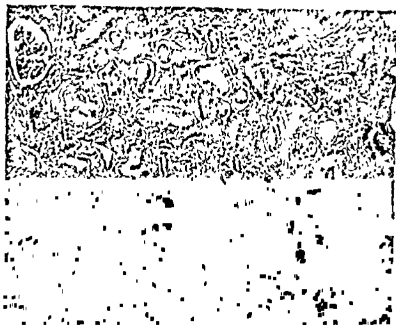


Fig. 25 Chronic pyelonephritis with diffuse interstitial scarring and marked thickening of the blood vessels. Photomicrograph Low power.

tissue Later, the interstitial tissue is infiltrated with lymphocytes, plasma cells, monocytes, and neutrophils. In the diseased areas of the medulla there is an increase in fibrous tissue (Fig. 25) The collecting tubules are either normal or dilated with atrophic epithelium and their lumens are filled with colloid-like casts The tubules in the cortex show similar changes (Fig. 26).

The glomeruli are reduced in number. Periglomerular fibrosis is present The glomerular tufts undergo fibrosis which finally become hyalinized Fibrosed glomeruli are seen in the wedge-shaped, atrophic areas in the renal cortex.

In glomerulonephritis, the primary change is a diffuse involvement of the glomeruli by an active or healed inflammatory process (Figs. 27, 28) In nephrosclerosis, the first and fundamental change is arteriolar sclerosis (3) (Figs 29, 30).

Vascular changes from the normal may be prominent in diseased portions of the kidney in chronic pyelonephritis. Varying degrees



Fig. 26. Chronic pyelonephritis. End stage. Extensive tubular dilatation with proteinaceous casts. Marked obliteration of glomeruli and severe vascular thickening. Note the resemblance to thyroid tissue. Photomicrograph. Low power.

of sclerosis occur in the arteries. The connective tissue of the intima is increased. There is reduplication of the internal elastic membrane and hypertrophy and fibrosis of the media. The walls of the arterioles are thickened as a result of concentric cellular proliferation. The smooth muscle is replaced by collagen. At times, there is arteriolar necrosis and acute arteriolitis.

The vascular changes in chronic pyelonephritis are proliferative rather than degenerative. In the absence of hypertension, these blood vessel lesions are present only in the scarred areas of the kidney. When hypertension exists, the blood vessel changes are more prominent and more diffuse (4, 6).

These severe departures from the normal in the kidney caused by chronic pyelonephritis end in a progressive destruction of functioning renal tissue.



FIG. 27 Chronic glomerulonephritis. A 24-year-old patient who died in uremia. Diffuse involvement of the glomeruli with crescent formation, interstitial inflammation and scarring Photomicrograph. Low power.



FIG 28 Chronic glomerulonephritis A 43-year-old male with hypertensive cardiac disease. Death in uremia Both kidneys are swollen with granular surfaces. Autopsy specimen



FIG 29 Malignant nephrosclerosis Vascular disease is the dominant feature with occasional obliteration of glomeruli Marked concentric lamination of the arteries Photomicrograph Low power

Bacteriology

Since pyelonephritis means that bacteria have invaded the kidney, the bacteriology of this disease is of importance. Identification of the infecting organisms is essential in treatment and prognosis This is not always a simple task for often in chronic pyelonephritis urine cultures are sterile and yet smoldering infection may exist in the kidney.

The bacteriology of chronic pyelonephritis is extremely variable. Many times, cultures of the urine are reported no growth but, intermittently, pathogenic organisms may be cultured. Repeated cultures and gram stains of the urinary sediment are necessary to determine whether there is active renal infection. Infections caused by cocci or bacilli are readily differentiated by microscopic examination of the stained urinary sediment. This is an aid in



FIG. 27. Chronic glomerulonephritis. A 24-year-old patient who died in uremia. Diffuse involvement of the glomeruli with crescent formation, interstitial inflammation and scarring. Photomicrograph. Low power.



FIG. 28. Chronic glomerulonephritis. A 43-year-old male with hypertensive cardiac disease. Death in uremia. Both kidneys are swollen with granular surfaces. Autopsy specimen.



FIG 29. Malignant nephrosclerosis Vascular disease is the dominant feature with occasional obliteration of glomeruli Marked concentric lamination of the arteries Photomicrograph Low power

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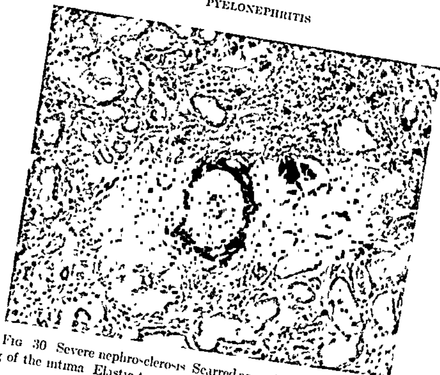


FIG 30 Severe nephrosclerosis Scarred area. An artery with thickening of the intima Elastic tissue stain Photomicrograph. Low power.

immediate therapy. Effective treatment, however, depends upon specific identification of the infecting bacteria and their sensitivity to antibacterial agents. The bacterial population in this disease often changes from organisms that are susceptible to therapy to those that are resistant to all practical antibacterial agents. This is particularly true when various drugs have been administered

In uncomplicated infections, bacteria of the colon group are the most frequent offenders. When the situation is complicated by obstructive lesions of the genito-urinary organs or other factors that favor infection, mixed bacterial populations are common. Urine cultures that show the presence of more than one type of bacterial growth usually signify chronic or complicated infections In long-standing infections, pure cultures are obtained in only about 20 per cent of cases When chronic pyelonephritis is complicated by the many factors that favor infection, the prevailing

TABLE 7

Bacteriology of Chronic Pyelonephritis, Massachusetts General Hospital, 1948–1956

Organism	No of Cultures
E coli	238
Staphylococci	22
Streptococci	14
B proteus	27
B pyocyaneus	15
Mixed bacteria	446
H influenzae	2
No growth	53
Not done	34
Total	871

organisms often are *B proteus*, *P aeruginosa*, *A aerogenes*, staphylococci, and streptococci These organisms are apt to be resistant to treatment and they usually cause the most severe degrees of damage to the kidney Mixed infections notoriously resist successful treatment Urea splitting bacteria such as *B proteus*, *P aeruginosa* and some strains of *E coli*, staphylococci and *Haemophilus influenzae* favor calculous formation (7–9)

The bacteriology of chronic pyelonephritis over nearly a decade in our own experience is given in Table 7

From the figures in Table 7 it is apparent that in cases of chronic pyelonephritis cultures of several types of organisms predominated This is quite different from the cultural characteristics of acute pyelonephritis where one type of organism, usually *E coli*, was the rule Mixed bacterial populations were commonest in the cases of complicated pyelonephritis Many of the mixed infections were identified as *E coli* with *B proteus* or *B pyocyaneus*, or all three, and most of such infections were resistant to antibacterial treatment Many of our cases of chronic pyelonephritis with a sterile urine were in such an advanced stage of the disease that they died in uremia and the diagnosis was made only at postmortem examination

Symptoms

It has been said that the disarming lack of symptoms of chronic pyelonephritis has obscured its seriousness and has favored its tendency to progress to fatal termination. If one reviews the histories and autopsy reports of these cases, the truth of this statement becomes evident (9).

A woman of 63 entered the hospital with a diagnosis of uremia She had been well until two years before with no urinary symptoms except for some frequency. During the past two years she had been anemic. Episodes of nausea and vomiting had been frequent.

At her first hospital admission her blood pressure was 155/90, Hgb , 11 8, N.P.N., 80-250 mg per cent. Her urine was infected with *E. coli* and *B. proteus* by culture. Blood chemistries: Na, 125 ; Cl, 83, K, 6.4; CO_2, 17.

It was thought that she had a salt-losing syndrome because of chronic pyelonephritis so she was put on a high sodium chloride intake On this, she did very well and was able to go abroad.

Two years later she returned to the hospital in congestive failure with an enlarged heart Her N.P N. now was 120 mg per cent With medical treatment she did quite well but within a year the blood pressure had risen to 215/115 and she was having seizures, probably hypocalcemic for the serum Ca was 5 8 per cent and the P 6 0 mg per cent.

On x-ray examination, there was osteoporosis and a compression fracture of T5 The serum creatinine was 9 8 mg. per cent. She could concentrate her urine to only 1 010. Shortly after, she died in uremia.

An autopsy, there was severe renal damage from chronic pyelonephritis, parathyroid hyperplasia, osteitis fibrosa cystica and cardiac hypertrophy (Fig. 31.)

Many patients with chronic pyelonephritis have had no evidence of active renal infection and have had no local symptoms. Often, medical advice was sought becuase of pallor, lassitude, weight loss, and easy fatigability. No other symptoms may be present until renal failure takes place with anemia and azotemia. Azotemia may be unsuspected for years.

There may be no history of past acute infection or illness to suggest acute pyelonephritis although vesical irritability has been

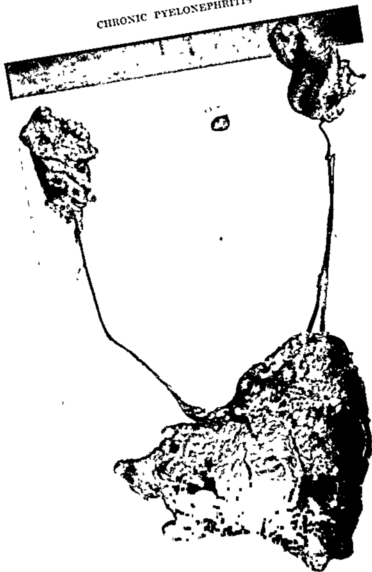


FIG 31 Chronic pyelonephritis with salt-losing syndrome S kidneys Double left ureter with bladder Death in uremia specimen

a common complaint. Bacilluria, albuminuria, and pyuria may occur in the absence of symptoms and where no structural abnormalities of the urinary organs are present. Urinary abnormalities, however, may be detected only during episodes of acute infection (10). In their review of chronic pyelonephritis, Nesbit and Conger (11) reported cystitis as an initial symptom in 68 per cent of cases and costovertebral pain in 17 per cent. Symptoms varied in duration from 3 months to 20 years. Of their patients, 75 per cent had some degree of renal impairment and in 25 per cent this was marked.

When chronic pyelonephritis is associated with obstructive lesions, operative procedures, or other urinary tract abnormalities, the causes of renal infection are evident and symptoms are continuous or intermittent until the underlying lesion is corrected. In such instances, symptoms often are so severe that urinary diversion or nephrectomy is necessary.

There are many conditions and diseases that are associated with, or that may lead to, chronic pyelonephritis. Urinary obstruction caused by calculous disease often is complicated by renal infection. Stones in the kidney can obstruct part of the calyceal system (Fig. 32). Severe obstruction results from calculi impacted in the ureter with, at times, destruction of a kidney (Figs. 33, 34, A and B). Hydronephrosis with infection often results from congenital abnormalities such as a narrowing of the ureter at its junction with the renal pelvis (Fig. 35) or from abnormalities of the renal blood supply (Fig. 36, A and B).

Obstructions of the lower urinary tract may be the cause of chronic infection and severe renal damage.

A 12-year-old boy was admitted because of urinary retention and persistent vomiting. Enuresis had always been present and he had been anemic and underdeveloped.

His urine was of low specific gravity, 1.006, with albumin 1 plus, many leukocytes in the sediment and *S. albus* and *E. coli* on culture. The N.P.N. was 160 mg. per cent. Urea clearance low. Serum chlorides, 109, sodium, 140.9, CO_2, 18.4. P.S.P., 25 per cent in two hours. Blood pressure, 130/80.

He was uremic but on catheter drainage he improved and the



FIG 32 Pyelonephritis and renal calculi Stones in the lower portion of the left kidney with caliectasis Cured by resection of the lower pole of the kidney Intravenous pyelogram

N P N dropped to 48 mg per cent An intravenous pyelogram demonstrated bilateral hydronephrosis and a retrograde right pyelogram demonstrated the renal situation (Fig 37, A) Residual urine was 550 ml

At cystoscopic and panendoscopic examination a congenital valve of the posterior urethra was found After the valve was resected he voided well, renal function improved, blood chemistries became normal and his infection cleared

At the age of 20 he was doing well in college, had a sterile urine and normal kidneys by intravenous pyelography (Fig 37, B)

Vesical dysfunction caused by lesions of the central nervous system is a well recognized cause of urinary obstruction, infection and impaired renal function (Fig 38)



FIG 33 Chronic pyelonephritis and right ureteral calculus Hydroureter and hydronephrosis. *B proteus* infection Right nephroureterectomy Retrograde pyelogram.

Malignant disease of the urinary tract or of adjacent structures, such as carcinoma of the ureter (Fig. 39) and carcinoma of the cervix, may be a cause of poor urinary drainage and renal damage, as in the following case

A woman of 50 had a Wertheim operation for cancer of the cervix After operation severe left flank pain developed with chills

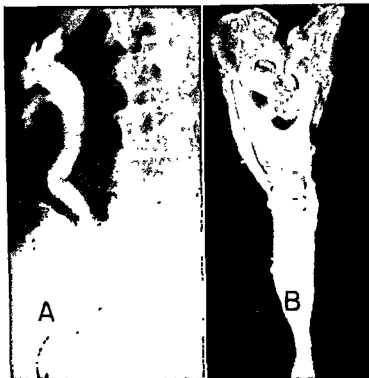


FIG 34 Chronic pyelonephritis with nonopaque calculus in the lower right ureter *E coli* infection A Right retrograde pyelogram B Nephroureterectomy. Complete destruction of the kidney Surgical specimen

and fever Urine cultures, *E coli*, *B pyocyaneus*, *B proteus* and nonhemolytic streptococci The left kidney was grossly diseased, its ureter was dilated from obstruction in the pelvis Nephrostomy was first performed and when her condition had improved, the left kidney was removed (Fig 40, A and B)

Polycystic disease of the kidneys when complicated by infection is serious and may be fatal (Fig 41, A and B)

Some generalized conditions and metabolic disorders affect the kidneys and often are associated with chronic pyelonephritis Lupus erythematosus is an example (Fig 42)



FIG 35 Stricture of left ureteropelvic junction and hydronephrosis. Chronic pyelonephritis Left nephrectomy. Retrograde pyelogram

Metabolic disorders also may cause serious renal damage. An example is hyperparathyroidism.

A woman of 50 had been operated upon three months before and a giant cell tumor beneath the right eye was removed. Frequent and urgent urination and anorexia recently had been present. Serum calcium, 11 2, phosphorus, 3 6, phosphate, 16 0 units.

Flaky calcification was present in both kidneys and renal func-

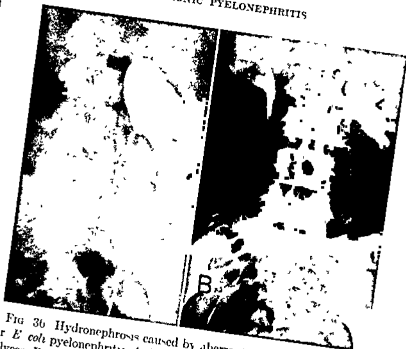


Fig 36 Hydronephrosis caused by aberrant artery crossing the ureter *E coli* pyelonephritis A Marked dilatation of left renal pelvis and calyces Retrograde pyelogram B Postoperative result 3 months after excision of abnormal artery and nephropexy Intravenous pyelogram

tion was impaired The bones were decalcified Diagnosis, hyperparathyroidism (Fig 43)

An example of severe renal damage that may result from chronic pyelonephritis is seen in the following

In 1941 a 28-year-old girl was seen complaining of frequent urination and nocturia Bilateral flank pain had been present for four months associated with the passage of gravel in the urine She always had been quite small Blood chemistries serum calcium, 9 7, phosphorus, 2 2, phosphatase, 4 8, N P N , 16 mg per cent, CO_2, 18 The urine could be concentrated to only 1 010, albumin, 1 plus, *E Coli* on culture On x-ray examination, there was dense calcification throughout the parenchyma of both kidneys (Fig 44) Dr Fuller Albright believed the course of events was chronic

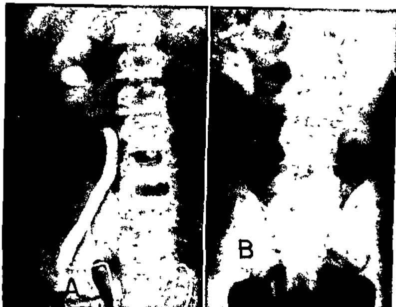


FIG 37 Congenital valve of posterior urethra Chronic pyelonephritis A Dilated right ureter and right hydronephrosis Retrograde pyelogram B Intravenous urogram 8 years after resection of posterior urethral valve Normal renal function

pyelonephritis with calcification of healed lesions in the renal parenchyma This resulted in tubular damage and an inability to form ammonia The result was acidosis, impairment of growth and hypophosphatemia due to the chronic acidosis. Diagnosis, nephrocalcinosis

The acidosis was well controlled with sodium citrate and in 1952, eleven years later, her condition was no worse.

Renal tubular acidosis may result in the deposit of calcium in the kidneys, infection and progressive renal damage (Fig. 45).

Chronic pyelonephritis occasionally occurs as a complication of severe respiratory tract infections.

A woman of 38 had had influenza in 1914 She began to have repeated attacks of renal colic 18 years later and passed many small stones She had an infected urine of low specific gravity (1.008-



FIG 38 Cord bladder and chronic pyelonephritis The right kidney is becoming progressively smaller Severe mixed urinary infection, *B. proteus*, *E coli*, *S aureus* Bilateral retrograde pyelograms

1 012) and a pure culture of *H influenzae* Serum calcium, 13 0, phosphorus, 3 7, phosphatase, 3 2, N P N , 47 mg per cent

Retrograde pyelograms showed blunted renal calyces and multiple calcifications in their walls Diagnosis, nephrosclerosis (Fig 46)

There are, therefore, many conditions, abnormalities and diseases that serve as a background for renal infection and chronic



Fig 39. Carcinoma of ureter and chronic pyelonephritis Filling defect in right mid-ureter with moderate hydronephrosis. Nephro-ureterectomy Retrograde pyelogram.

pyelonephritis. Some respond to treatment but many are incurable.

Chronic pyelonephritis has been responsible for some instances of unexplained hematuria and roentgen examination often shows no visible abnormality.

A weak and tired woman of 79 had had hematuria for six months.

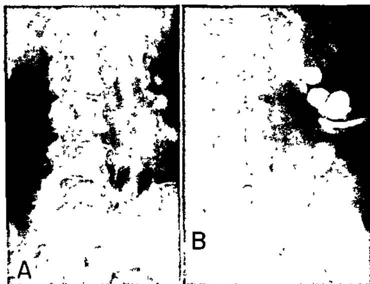


FIG 40 Carcinoma of cervix and pyelonephritis A Severely damaged left kidney from ureteral obstruction and infection Intravenous urogram B Left nephrostomy previous to nephrectomy Retrograde pyelogram

Upon admission her Hgb was 7 8 gm N P N , 30 mg per cent, blood pressure, 115/65 General physical examination was normal Urine culture, nonhemolytic streptococci.

At cystoscopic examination blood was seen coming from the right ureter A retrograde right pyelogram showed dilatation of the pelvis and calyces of a low kidney (Fig 47) The left kidney was normal

Because of the persistent and profuse bleeding the right kidney was removed On pathological examination there was moderate nephrosclerosis, erosion of the mucosa of the upper calyx with recent and old hemorrhage, and a well-marked inflammatory reaction from acute and chronic pyelonephritis

During the course of chronic pyelonephritis, therefore, symptoms may be absent or slight or referable to organs other than the kidney Poor health may be the chief complaint In spite of



Fig. 41. Polycystic kidneys and pyelonephritis. A woman of 65 with bilateral abdominal masses, hypertension (blood pressure 200/110) and severe sepsis. *E. coli*, *B. proteus* and nonhemolytic streptococci in the urine. Death in uremia. A. Both kidneys enlarged with typical crescentic filling defects and widely separated calyces. Retrograde pyelograms. (See Fig. 41, B.)

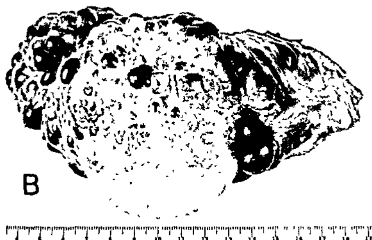


FIG 41 Polycystic kidneys and pyelonephritis B Gross autopsy specimen The kidney is riddled with infected cysts. (See Fig 41, A)

treatment, pyuria and bacilluria sometimes persist Whatever symptoms may exist often are present for long periods of time (Fig. 48). The end is renal failure and death The course of chronic pyelonephritis is unpredictable, for some cases heal (7, 8) (Fig 49)

Diagnosis

Cases of uncomplicated chronic pyelonephritis that give no history of acute or recurrent episodes of renal infection can be diagnostic problems This is especially true of those patients who first present themselves with advanced renal failure In the past, the diagnosis frequently was chronic glomerulonephritis Even today it is not unusual that a correct diagnosis is reached only at postmortem examination Many clinical and laboratory procedures may be necessary to arrive at the truth

Tests of Renal Function

These have an important place in the clinical investigation of these patients The P S P test is of value since this dye is excreted



FIG 42 Lupus erythematosus and chronic pyelonephritis A woman of 50 with uncontrolled *E. coli* urinary infection. The calyces of both kidneys are distorted Intravenous urogram

specifically by the renal cells (12). The P.S P. test and the estimation of urea in the blood opened a new field in the study of renal disease. A continued low urea clearance means serious derangement of renal function. When the concentration of creatinine in the blood rises significantly, renal damage is severe. Inadequate excretion of the organic iodine compounds indicates ineffective renal plasma flow (13).



FIG 43 Hyperparathyroidism and chronic pyelonephritis Flaky calcification is present throughout both kidneys The bones are decalcified Renal function is poor Intravenous urogram

In chronic pyelonephritis, diminished tubular function dominates the picture and in terminal renal failure there is a marked reduction in all functioning renal units (14)

Urine Examination

The excretion of abnormal quantities of urine may be an indication of renal impairment especially when the specific gravity is



Fig. 44 Chronic pyelonephritis and nephrocalcinosis Calcium de-posits are present in the parenchyma of both kidneys. Plain film

fixed between 1.005 and 1.012 The continual presence of sig-nificant amounts of albumin in the urine also is an indication o abnormal renal function.

The finding of a moderate number of bacteria in the urine by stained smear is suggestive of significant bacteriuria (15) and quantitative bacterial counts, using the agar plate technic, are said to provide a reliable indication of infection. Bacteriuria ap-proximating 1000 viable organisms per ml. of urine is considered



FIG 45 Renal tubular acidosis and chronic pyelonephritis Calcium deposits in the parenchyma of both kidneys Fair renal function Intravenous pyelogram

to be necessary for a certain diagnosis of infection Repeated urine cultures may be needed to prove that active infection is present.

X-ray Examination

A combination of urological investigation and roentgen examination usually is necessary during the study of patients with chronic pyelonephritis If renal function is adequate, intravenous



FIG. 46 Chronic pyelonephritis and nephrosclerosis caused by *H. influenzae* The renal calyces are blunted and calcium is deposited in their walls Retrograde pyelograms.

urography alone may suffice. Otherwise, retrograde pyelography should be performed to make an accurate diagnosis of the renal lesion

Renal deformities caused by chronic pyelonephritis may be evident by either intravenous or retrograde pyelography. Early changes are irregularities of the calyceal system, often with some blunting (Fig. 50). Later changes consist of further calyceal



FIG 47 Hematuria from chronic pyelonephritis The right renal pelvis and calyces are dilated The uppermost calyx is a little irregular Retrograde pyelogram

dilatation and narrowed infundibuli One or both kidneys become reduced in size (Fig 51). When the disease has been severe or of long duration the evidence of severe renal damage is clear with marked deformities of the renal pelves and calyces, complete loss of the normal architecture and shrinkage of kidney substance. Hypertension and uremia follow (Fig 52)



FIG 48 Chronic pyelonephritis of 32 years duration. The calyces of the right kidney are irregularly dilated and deformed. The left kidney also was diseased Persistent staphylococcus infection Retrograde pyelogram

The pyelographic changes of chronic pyelonephritis sometimes resemble those of renal tuberculosis with calyceal contraction and ureteral dilatation.

A boy of 15 was admitted because of right flank pain for six months and a 30-lb. weight loss. The left kidney was normal. The



Fig 49 Healed chronic pyelonephritis The calyces of both kidneys are somewhat irregular Sterile urine Retrograde pyelograms

right kidney was somewhat large and the upper calyx was narrowed and elongated The right ureter was dilated These changes were suggestive of tuberculosis (Fig 53)

The right kidney was removed On pathological examination there was acute and chronic pyelonephritis

Cystography and post-voiding cystograms may be indicated, particularly in children In hypertensive patients, translumbar



FIG 50 Early chronic pyelonephritis The upper calyx of the right kidney is dilated and irregular The lowest calyx also is abnormal Urine culture, *E coli* Intravenous urogram

aortography will help to differentiate occlusions of the renal blood supply associated with pyelonephritis as a cause of an existing hypertension.

Renal Biopsy

Tissue from the kidney for microscopic examination can be obtained at operation or by needle puncture. Biopsy is the most



FIG 51 Advanced chronic pyelonephritis Beginning hypertension Both kidneys are grossly abnormal Some calyces are dilated The infundibuli are narrowed and drawn out The right kidney is quite small Retrograde pyelograms

accurate diagnostic procedure Not only can the histology of the diseased kidney be studied, but the bacteriology of the infection may be determined, at times, by cultural methods Positive cultures have been obtained in this way when urine cultures have been persistently negative



FIG. 52 Severe chronic pyelonephritis. A man of 28 with long-standing disease and considerable renal damage. *B. pyocyaneus*, *B. proteus* and *E. coli* in urine Blood pressure, 170/70 Impending uremia. Retrograde pyelograms

Needle biopsy, although in its early stages of use and development, has been exceedingly useful in the differential diagnosis of many renal lesions. It is not advised when a kidney is hydronephrotic or when neoplasm is suspected.

When it is properly performed, needle biopsy seems to entail a



FIG 53 Chronic pyelonephritis resembling tuberculosis The upper calyx of the right kidney is narrowed The ureter is dilated Oblique retrograde pyelogram

minimum of risk Thus, in 200 cases, Kark *et al* (16) had only transient renal colic from clots in the ureter in five patients There were no serious complications

Certain precautions must be taken to make needle biopsy a safe procedure All patients should be in a hospital Preliminary studies consist of examination of the urine with cultures, hema-

tological studies, intravenous urography to determine kidney position, N.P.N. and P.S.P. determinations and properly typed blood set-up for a possible transfusion. The actual technic of the procedure has been well described by Muehrcke *et al.* and others (17–20). In the future, this procedure doubtless will be employed more frequently.

In addition to these clinical procedures focused upon the kidney, a complete examination of patients suspected of having chronic pyelonephritis should include studies of the heart by x-ray films and electrocardiograms, examination of the eye grounds, complete blood studies, and serum electrolyte determinations If this disease is kept in mind in chronically ill patients who are diagnostic problems, there should be more accurate diagnoses made at the bed-side.

Treatment

It has been said that the failure to recognize the importance of the early stages of pyelonephritis in childhood, the puerperium and in urological lesions has resulted in a lack of continuity in the management of this disease and has done much to prevent a complete cure of the initial infection (9). This statement is quite true, I believe, and is in agreement with what has often been said, that the best chance of curing chronic pyelonephritis is when it is acute. Every effort should be made to lop- ment of this disease.

Successful treatment depends h of the history, course, gross bacteriology of chronic pyelo fection should be studied. T upon the duration and stage erence to blood-vessel change r dence of active infection, tog the patient.

It is generally agreed tha phritis is unsatisfactory. Onl to have responded well to response is not clear but it

changes in the interstitial tissue of the kidney and the type of infecting organisms. The discovery and use of the new antibiotics have not significantly diminished the number of cases of chronic pyuria and bacilluria (10).

When active renal infection has been demonstrated, aggressive antibacterial treatment is indicated. The drug to be used will depend upon bacterial identification and sensitivity tests. Even when the active infection has cleared, prolonged administration of some antibacterial agent in small doses seems advisable. At present, one of the soluble sulfonamides is preferable to a long course of antibiotic therapy. Treatment with antibiotics is not devoid of risk. The chief hazards of antibiotic therapy are anaphylactic reactions, superimposed serious staphylococcal infections and blood dyscrasias (21). The presence of some antibacterial agent continually in the urine over long periods of time may help to prevent recurring episodes of acute renal infection and may lessen the chances of severe kidney damage.

The results of the treatment of 903 cases of chronic pyelonephritis at the Massachusetts General Hospital over a 9-year period are given in Table 8. Only about one-fifth of our patients

TABLE 8

Chronic Pyelonephritis, Results of Treatment in Massachusetts General Hospital, 1948–1956

Year	No. of Cases	Cured	Not Cured	Died in Uremia
1948	146	33 (22.6)*	113 (77.4)	32 (21.9)
1949	64	23 (36.0)	41 (64.0)	8 (12.5)
1950	91	12 (13.2)	79 (86.8)	24 (26.4)
1951	118	24 (20.0)	94 (80.0)	22 (18.7)
1952	77	18 (23.4)	59 (76.6)	20 (26.0)
1953	116	24 (20.7)	92 (79.3)	21 (25.8)
1954	93	24 (25.8)	69 (74.2)	21 (22.5)
1955	98	25 (25.5)	73 (74.5)	8 (8.2)
1956	100	19 (19.0)	81 (81.0)	17 (17.0)
Total	903	202 (22.3)	701 (77.7)	173 (19.1)

* Figure in parentheses is percentage.

could be classified as cured and this is probably an optimistic estimate for I had no way of knowing, in many instances, whether infection had recurred. Criteria of cure were normal urine, sterile cultures, and lack of symptoms. It is quite evident from these figures that our ability to cure chronic pyelonephritis has shown no significant improvement over the years of administration of the recent antibacterial agents

Prognosis

The outcome of chronic pyelonephritis depends upon the duration of the disease, extent of renal damage, types of bacteria present, and their susceptibility to drug therapy. Complicated cases may be impossible to cure, for although infection seems to be eliminated in many instances, recurrences are common. If only one kidney is diseased, surgery may provide a possible step toward cure, sometimes by the loss of the diseased organ Complicated cases offer a better chance of cure than uncomplicated cases if renal damage is not excessive, *if the underlying lesion can* be corrected, and if the invading bacteria are sensitive to medication.

Even if the urine becomes normal and there are no symptoms, infection can persist in the interstitial tissues and acute flare-ups may take place after months or years of quiescence Some patients continue to have pyuria, bacilluria, and albuminuria that persist in spite of treatment and with a slow progression of renal damage that extends over many years. Some of these patients lead active lives for years unaware of their affliction. Others complain of weakness and feel generally poorly. Many finally die in uremia.

When there is renal *insufficiency or hypertension or a combination* of the two, the prognosis is poor (8). Nothing will restore *irrevocably damaged* renal units.

The prognosis of chronic pyelonephritis depends chiefly upon the *effective* treatment of acute pyelonephritis.

A study of chronic pyelonephritis necessitates dividing these cases into two classes. (a) those with complicating lesions such as calculi, urinary tract obstructions and operative procedures upon other systems that affect the integrity of the urinary organs; and (b) uncomplicated infections.

TABLE 9

Complicated and Uncomplicated Cases of Chronic Pyelonephritis, Massachusetts General Hospital, 1948–1956

	No of Cases	Cured	Not Cured	Died in Uremia
Complicated	538	149 (27 7)*	389 (72 3)	79 (14 7)
Uncomplicated	365	53 (14 5)	312 (85 5)	94 (25 7)

* Figure in parentheses is percentage

The frequency of urinary disorders following radical surgical operations upon the pelvic viscera is well known Such complications are especially prominent after cystectomy hysterectomy, and abdominoperineal operations for malignant disease. Lesions of the central nervous system, such as spinal cord injuries, poliomyelitis, and some generalized diseases, often have a serious effect upon bladder and kidney.

Pyelonephritis resulting from these complicating factors should be separated from pyelonephritis where none of these lesions exists In many instances of complicated pyelonephritis the disease can be cured by the elimination of the complicating factor. So the mortality and morbidity in such cases should be lower than in uncomplicated cases. The treatment of uncomplicated chronic pyelonephritis is notoriously unsatisfactory and usually has little or no effect in the late stages of this disease Uncomplicated chronic pyelonephritis presents the real challenge to the physician

These facts are presented in Table 9

The figures in Table 9 indicate that chronic pyelonephritis, complicated by other abnormal conditions, has a better chance of cure and less chance of death in uremia than uncomplicated pyelonephritis provided that the complicating factor can be corrected

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8

PYELONEPHRITIS IN INFANCY AND CHILDHOOD

Pyelonephritis, in its many aspects, has one of its greatest impacts in the early years of life. During this period, its incidence is high because of the frequency of congenital defects of the genito-urinary organs. Its symptoms often are generalized and difficult to interpret. Its course many times is prolonged. Its pathology has been well described. Treatment, many times, is ineffective. Its ravages can be extreme.

> A girl of 4 had a history of irritability, episodes of high fever, vomiting, and right sided abdominal pain for 18 months. Pyuria had been present. She had not done well on sulfonamide therapy, was weakly, and had enuresis.
>
> Upon admission to the hospital, the temperature was 99.0°, blood pressure, 90/50, W.B.C., 9,600, N.P.N., 24 mg. per cent, Hgb., 10.9 gm. Urine specific gravity, 1.018–1.020, albumin, 0, sediment, few W.B.C., culture, no growth. Urea clearance, 54 per cent of normal.



FIG 54. Recurring pyelonephritis. The right kidney is abnormal with dilatation of the pelvis and deformed, ragged calyces. Retrograde pyelograms

By intravenous pyelography the left kidney was normal but the right renal pelvis and ureter were dilated (Fig 54). At cystoscopic examination, the bladder and urethra were normal, no residual urine was present and there was no ureterovesical reflux. Urine cultures were persistently negative

The patient was put on chloramphenicol and followed in the Out-patient Department. During the next 2 years she had 8 ad-

missions to the hospital for recurring attacks of chills, fever, and abdominal pain in spite of long continued antibiotic treatment Pyuria continued, *B proteus* was cultured from the urine, then *E coli* and beta hemolytic streptococci were identified

After 3 years of care, observation and continued therapy, the right hydronephrosis was unchanged but the left kidney calyces now were dilated Urine cultures, at times, were positive for various organisms· *E coli*, *B pyocyaneus*, *S aureus* and alpha hemolytic streptococci No treatment permanently eliminated the infection After 7 years of therapy renal function was still good but the episodes of chills and fever continued

This case is an example of how ineffective recent antibacterial treatment may be in chronic pyelonephritis in infancy and childhood.

Much of our knowledge concerning pyelonephritis has come from the study of children who had this disease. Its seriousness, frequency, and importance in the young was recognized and written about over 30 years ago These authors deserve great credit for bringing to general attention a disease that had been little understood in the past, was seldom recognized, and was not treated with enough aggressiveness (1–13) All agreed that obstruction to free urinary flow was a predisposing cause of infection Some believed that acute pyelonephritis could be a complication of upper respiratory tract infections Foci of infection such as tonsils, adenoids, sinuses, teeth, gums, and middle ears were considered by certain writers to be important factors in the genesis of pyelonephritis In reviewing the records of recurrent pyelonephritis in children it did seem that renal infection often followed disease in these areas

The commonest obstructive lesions in the early years of life were strictures of the ureter (Fig 55), aberrant blood vessels, calculi, peri-ureteral masses or inflammations, contractions of the bladder outlet, posterior urethral valves, narrowings of the urethral meatus, and gross abnormalities of development

A 12-year-old boy with enuresis began having chills and fever 8 months before admission to the hospital Voiding always had been difficult



FIG 55 Stricture of the ureter and pyelonephritis Right hydronephrosis from congenital narrowing of the upper ureter. A girl of 12 Retrograde pyelogram

His general condition was only fair. Blood pressure, 118/78, N.P.N., 33 mg. per cent; creatinine, 1.2 Other chemistries were normal An infected urine cultured *E. coli*, *B. proteus* and *B pyocyaneus* Residual urine, 150 ml.

A voiding cystogram demonstrated bilateral ureterovesical reflux and hydronephrosis and a funnel-shaped posterior urethra (Fig 56, A). On cystoscopic and panendoscopic examination posterior ure-

thral valves were seen These were removed by transurethral resection

He then voided well and 18 months later an intravenous pyelogram, after reimplantation of the ureters, showed an improvement in both kidneys (Fig 56, B)

Gross abnormalities of development may seriously affect the urinary organs in early life with infection, renal damage, and uremia This may occur as a complication of meningomyelocele

An 8-day-old male infant came to the hospital with a large lumbar meningomyelocele He was severely ill with high fever, pyuria, and a blood culture positive for *E coli* The same organisms were present in the urine Under treatment the blood stream infection and the



Fig 56 Posterior urethral valves A Voiding cystogram Bilateral vesicoureteral reflux and hydronephrosis B Eighteen months after resection of the valves and reimplantation of the ureters Intravenous urogram



FIG 57. Meningomyelocele and pyelonephritis A. An 8-day-old boy with this congenital abnormality. Plain x-ray film B. Hugely dilated ureters and renal pelves at the age of 3. Death in uremia at the age of 11. Cystogram.

acute pyelonephritis subsided, and the defect in the spinal cord was repaired (Fig 57, A)

The subsequent course was one of repeated episodes of pyelonephritis The blood pressure rose to 208/148. *E. coli* and nonhemolytic streptococci were cultured repeatedly from the urine

At the age of 3 a cystogram showed bilateral reflux up both ureters and hugely dilated ureters and renal pelves (Fig 57, B). The urinary tract infection with *B. proteus* and *B. pyocyaneus* could not be controlled The nonprotein nitrogen rose to 250 mg per cent and he died in uremia at the age of 11.

Postmortem findings were severe acute and chronic pyelonephritis

Of 65 children at the Massachusetts General Hospital aged 10 or under who had recurrent or chronic pyelonephritis, 28 or about 43 per cent had some abnormality of the urinary organs. So, with

any child who has chronic pyelonephritis, the chances are about even that the urinary tract will be abnormal

The following case report illustrates the severe renal damage that resulted from a congenital abnormality and chronic pyelonephritis.

> An 8-year-old girl had a congenital stricture of the right ureter complicated by an infected hydronephrosis Two cutaneous ureterostomies had been performed with poor results and then a right nephrostomy was done.
>
> Upon admission to the hospital, her condition was good, total renal function tests were normal and the left kidney was normal
>
> A right nephroureterectomy was carried out and a worthless kidney was removed Pathological report a 58-gm kidney with severe chronic pyelonephritis (Fig 58)
>
> Three years later she was well with an uninfected urine

Pathology and Bacteriology

By careful study of the histological changes of "pyelitis" in children it became evident to early observers that the changes consisted of a true suppurative lesion of the interstitial tissues of the kidney Inflammatory foci often were adjacent to small blood vessels The smaller lesions healed without scar formation but the more advanced lesions led to necrosis and fibrous tissue formation (6) (Fig. 59)

The relation of chronic pyelonephritis and hypertension in children was described by Butler and Lanman (10) in 1937 Postmortem studies of 8 patients from 3 to 11 years of age revealed chronic pyelonephritis Systolic blood pressures in these children ranged from 140 to 250 and diastolic pressures from 110 to 170. Two had hypertensive crises and died of cardiac failure before there was significant nitrogen retention Of Butler's patients, 15 had had chronic pyelonephritis and hypertension before there was appreciable diminution of kidney function One boy of 7 was cured of his hypertension by nephrectomy Pyelonephritis was present in the removed kidney with moderate thickening of the media and intima of the smaller arterioles This was one of the

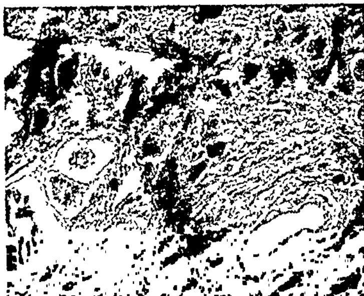


Fig 59 Severe chronic pyelonephritis with destruction of the kidney A child of 4 No normal renal elements Photomicrograph Low power

first reported cases of pyelonephritis and hypertension cured by nephrectomy.

An 8-year-old girl gave a history of vomiting and abdominal pain The urine contained many pus cells, albumin plus 1, culture, *S albus* At this time, the blood pressure was 110 80 She was treated for acute pyelonephritis but continued to have abdominal pain and pyuria

At the age of 13 the blood pressure had risen to 145 100 *E coli* was cultured from the urine An intravenous urogram demonstrated bilateral duplication of the ureters and renal pelves The two lower calyces of the right kidney were dilated (Fig 60, A) The urinary infection could not be eliminated by medical treatment and during the next two years the blood pressure rose to 160/110 Headaches occurred and there were repeated episodes of chills and fever Renal function tests remained normal

By abdominal aortography, both main renal arteries were normal



FIG 60 Double ureters and renal pelves Chronic pyelonephritis and hypertension in a 13-year-old girl. A. The lower calyces of the right kidney are dilated and chronically infected. Intravenous urogram. B. Lumbar aortogram visualizing normal main renal arteries and an accessory artery to the lower pole of the left kidney.

(Fig 60, B) There was an accessory artery to the lower pole of the left kidney

It was believed that the chronic infection in the lower portion of the right kidney was responsible for the acute episodes she had been having and that this might be a factor in the hypertension The urine now contained hemolytic streptococci resistant to all antibiotics.

The lower portion of the right kidney was resected. After operation the blood pressure was 134/94. Five years later she was well with a sterile urine, normal renal function tests, and a blood pressure of 134/88

Chronic pyelonephritis in children was a primary cause of death in approximately 2 per cent of 2043 autopsies, 63 per cent being under 2 years of age, 37 per cent from 2 to 12 years. *There was*

TABLE 10

Bacteriology of Pyelonephritis in Infancy and Childhood, Massachusetts General Hospital, 1948–1956

Organism	No. of Cases	Per Cent
E. coli	64	50.0
Staphylococci	4	3.2
Streptococci	3	2.4
B. proteus	9	7.2
B. pyocyaneus	0	0
Mixed	38	30.7
No growth	8	6.5
Total	126	100.0

an anatomical malformation of the urinary tract in 54 per cent of the infants and 79 per cent of the children (10). The high incidence of pyelonephritis in childhood and its seriousness in infants with or without anatomical abnormalities was emphasized and it was pointed out that pyelonephritis and not chronic nephritis was the commonest cause of renal insufficiency with uremia at these ages.

As in adults, the commonest infecting organism in pyel[illegible] phritis in infancy and childhood is *E. coli* (Table 10).

Of 126 cases of acute and chronic pyelonephritis in child[illegible] aged 10 or under at the Massachusetts General Hospital [illegible] responsible organism was *E. coli* in 50 per cent. Mixed infect[illegible] were high (30.7 per cent) and many of these were *E. coli* [illegible] staphylococci or streptococci as the organisms, in addition to *E. coli*. Perhaps some of these mixed cultures represented conta[illegible] tion in the collection of urine for culture in these young pat[illegible]. When *B. proteus* was encountered, either in pure culture [illegible] other bacteria, the infection usually was severe and d[illegible] control.

Symptoms

In infancy and childhood the symptoms of pyelon[illegible], acute or chronic, often are meager and misleading. Frequent [illegible]

urination with dysuria and occasionally hematuria, are common complaints. Loin pain may be present. The outstanding symptoms, however, are of the gastrointestinal tract in a great many of these young patients. Such generalized symptoms as the failure to gain weight, anemia, headache, apathy, and irritability may be the only real evidences of illness.

Enuresis in the young often has been the first complaint. Any child with enuresis should have the most careful studies made of the urinary tract since many times there is a background of infection, congenital abnormalities, and obstructive lesions as a real cause of the enuresis.

A woman of 24 had had enuresis since birth. When she was 18 years old, hematuria had occurred at intervals for a year, but no adequate studies were made.

On examination at the hospital, the blood pressure was 120/80 Soft masses were felt in the abdomen The urine was concentrated only to 1.010 Pyuria was present and *E coli* was cultured. P.S.P. test, 15 per cent in two hours

Retrograde pyelograms demonstrated huge hydronephrotic kidneys (Fig 61).

At operation, both ureters were strictured near the ureteropelvic junctions. The strictured areas were resected and the ureters were anastomosed Six months later there was clinical improvement.

This case is an illustration of the importance of enuresis in childhood and the necessity of adequate examination to determine its cause

When there is any degree of obstruction at the bladder neck or of the urethra there is straining and difficult voiding, usually apparent to the parents. Bed-wetting and dribbling may signify the overflow of a bladder that is always distended with urine and easily palpable (Figs. 62, 63).

Diagnosis

Pyuria so often is the only sign of kidney infection in the young that urinary infection always should receive serious consideration. When the infection is not thoroughly and permanently cleared by



Fig 61 Giant bilateral hydronephrosis Bilateral [illegible]
The first symptom was enuresis Retrograde pyelo[illegible]

adequate medical treatment complete phys[illegible]
investigation is in order This entails man[illegible]
repeated urinalyses, urine cultures and [illegible]
stains of the urinary sediment, renal functio[illegible]
serum electrolyte determinations, roentgen[illegible]
copy, panendoscopy, and circulatory and [illegible]



FIG 62 Spina bifida, neurogenic bladder, chronic pyelonephritis and renal rickets A girl of 12 with bilateral hydronephrosis caused by the vesical dysfunction Retrograde pyelograms

Only through such investigations can a real evaluation of the situation be made and an intelligent course of treatment be outlined.

Physical Examination



Fig 63 Renal rickets associated with spina bifida and severe renal disease Same case as Figure 62

child with chronic pyelonephritis often presents the picture of a chronically ill patient, dehydrated, anemic, febrile, and critically sick, but with few localizing signs Costovertebral tenderness may be present but more often abdominal tenderness is such that an intra-abdominal lesion is suspected The diagnosis wavers from early pneumonia or meningitis to any of the acute infections of childhood. No other signs may be present except pyuria and in either acute or chronic pyelonephritis the urine, at times, may be clear Repeated urinalyses, however, should provide a clue With proper technic, stains of the urinary sediment or urine cultures should show that an active infection exists and that it has not responded to medical treatment Then further investigation is indicated

Laboratory Tests

Typically, in chronic pyelonephritis there is an acid urine, acidosis, low CO_2, hyperchloremia and hyperkalemia In children, these values may mean renal tubular acidosis Here, there is apt to be nephrocalcinosis, hypophosphatemia and osteomalacia, and possibly, hypokalemia In uremia, hyperchloremia is not present. In addition to routine blood analyses, including hemoglobin,

smear, leukocyte count, nonprotein nitrogen or blood urea nitrogen, creatinine, CO_2 and sedimentation rates, serum electrolyte determinations should be carried out. These include values for calcium, phosphorus, potassium, sodium, and chloride.

Tests of Renal Function

In acute pyelonephritis the ability of the kidney to function efficiently is little, if any, impaired. When renal disease has been recurrent or long-standing, the kidney may be so severely damaged that it can no longer adequately perform its many functions Studies of renal function are especially important in chronic pyelonephritis.

As in adults, the first evidence of renal damage may be the passage of large amounts of dilute urine. The specific gravity of the urine becomes fixed at low levels, 1.010 to 1 014. The kidney is unable to concentrate the urine. The concentration tests measure tubular function. Rough estimates of renal function in children are provided by the blood levels of nonprotein nitrogen and urea nitrogen.

Normal ranges of plasma components as indicators of renal function (14) are reported in Table 11.

Plasma levels of creatinine are useful indications of renal insufficiency.

More delicate tests of renal function are the P.S.P. and urea concentration tests. At cystoscopic examination, the function of

TABLE 11

Normal Ranges of Plasma Components

	(mg %)
Nonprotein nitrogen	20–30
Urea nitrogen	10–15
Urea	10–40
Creatinine	0 5–1.5
Sulfate (inorganic)	0.3–0.6 mmoles/l
Sulfur (inorganic)	1.0–2 0
Phosphate (inorganic)	0.5–1.5 mmoles/l.
Phosphorus (inorganic)	1.5–4.5

each kidney can be roughly determined by the appearance and concentration of indigocarmine given intravenously (5 0 cc) and the ureteral orifices watched as this blue dye emerges from each ureter. Levels of nonprotein nitrogen of urine, secured by ureteral catheterization, also provide an indication of the function of each kidney The time of appearance and concentration of the organic iodine preparations for intravenous urography also serve as tests of renal function.

Roentgen Examination

In all cases of pyelonephritis in infancy and childhood, x-ray examination is essential The only possible exception might be a single mild episode of pyuria with fever that responds quickly to medical treatment. If acute episodes recur, or if pyuria persists, x-ray examination must be carried out In acute pyelonephritis x-ray examination usually shows no renal abnormality or, at the most, some slight impairment of function (Fig 64). In acute glomerulonephritis renal function is likely to be more depressed because of the more diffuse damage to the renal units (Fig 65)

Satisfactory plain x-ray films will detect abnormalities of bony structure such as osteomalacia, renal rickets, and spina bifida The renal outlines give some indication of the size, shape and position of the kidneys. If no renal outline is seen the kidney may be absent (Fig 66) Radiopaque shadows in the course of the urinary tract may be calculi

More satisfactory information concerning the urinary organs is provided by the administration of one of the organic iodine preparations, intravenously if practical, or subcutaneously in dilute form in infants Roentgen visualization provides the vitally needed information concerning abnormalities of the kidneys, ureters and bladder If adequate information is not secured by intravenous methods, retrograde pyelography should be carried out

Delayed or Voiding Cystograms

Reflux of urine from the bladder to the kidney through the lumen of ureter is an important factor in the genesis of pyelonephritis.



Fig 64. Acute pyelonephritis Normal right kidney Some delay in excretion by the left kidney Intravenous urogram

A 4-year-old girl had recurring attacks of left pyelonephritis following a virus infection The urine was infected with *E coli*, *S. albus* and alpha hemolytic streptococci present by culture. The bladder and urethra were normal by cystoscopic and panendoscopic examination

A cystogram demonstrated vesico-ureteral reflux up a double left ureter and some left calicectasis (Fig 67).



FIG 65 Acute glomerulonephritis Exudative changes involving all glomeruli Red blood cells within the tubules. Photomicrograph Low power.

The left ureter was reimplanted by the Politano-Leadbetter technic This cured the reflux, eliminated the infection and improved the function of the left kidney

This phenomenon probably occurs only in disease Vesicoureteral reflux has been known to occur in paraplegic patients and has been a recognized cause of recurrent pyelonephritis, failing renal function, and a major cause of shortened lives Only recently, has vesico-ureteral reflux been known to have somewhat the same significance in pyelonephritis of infancy and childhood (15)

By delayed or voiding cystograms in children, unsuspected abnormalities in children have been detected in the upper urinary tract when intravenous pyelography showed no abnormality This examination is essential in the study of pyelonephritis in children.



FIG. 66 Absent right kidney. The left kidney is large from compensatory hypertrophy The right side of the trigone was not present. Intravenous urogram

A 6-year-old boy had been operated upon elsewhere a year before and the left kidney removed for hydronephrosis. Attacks of acute pyelonephritis continued after operation.

His urine was infected but sterile on culture. Blood pressure, 120/60 Normal blood chemistries Residual urine, 40 to 50 ml.

An intravenous pyelogram was made and the right kidney was considered to be normal 68, (Fig A). A voiding cystogram *demon-*

strated bilateral vesico-ureteral reflux with considerable right hydronephrosis and dilatation and tortuosity of the remainder of the left ureter (Fig 68, B) By panendoscopic examination there was narrowing of the vesical outlet.

At operation, the dilated lower left ureter was removed A wedge resection of the bladder neck was performed and the right ureter was reimplanted into the bladder.



Fig 67 Vesico-ureteral reflux Chronic pyelonephritis Reflux up a double left ureter Left caliectasis Cystogram



FIG 68 Vesico-ureteral reflux and pyelonephritis A. The remaining right kidney was considered normal by intravenous pyelography (lateral) B A voiding cystogram demonstrates reflux on both sides with a dilated right renal pelvis and dilatation of the remainder of the left ureter after left nephrectomy. (See Figs 68, C and D)

> The postoperative result was gratifying Vesico-ureteral reflux no longer was present (Fig 68, C) and 18 months later there was considerable improvement in the right kidney by intravenous pyelography (Fig 68, D) The urine was sterile.

The technic of delayed cystograms is simple. Twenty-four hours after intravenous urography, 75 to 150 ml. of one of the preparations used for intravenous urography diluted to about 10 per cent is instilled into the bladder by catheter. The catheter is withdrawn and an x-ray exposure is made immediately. The patient then ambulates and x-ray films are taken at 30 and 60 minute intervals (16) This simple examination often is rewarding.



Fig 68 Vesico-ureteral reflux and pyelonephritis C Cystogram after reimplantation of the right ureter and removal of the left ureter No reflux D Intravenous urogram 18 months after operation Considerable improvement in the appearance of the remaining right kidney

Treatment

Acute uncomplicated pyelonephritis in children usually responds well to treatment It has been common practice to give one of the sulfonamides to these young patients unless urine cultures and sensitivity tests indicate that some other preparation is indicated Full doses of one of these drugs usually will control the initial acute infection and, if treatment is continued for several weeks with a reduced dose, the chances of an acute flare-up of infection seem to be lessened Just how long the reduced dose should be continued has not been settled but it would seem advisable to keep up some form of medication until repeated examinations of the urine, at intervals, have been normal (17)

The results of treatment of acute pyelonephritis at the Massachusetts General Hospital are given in Table 12

TABLE 12

Treatment of Acute Pyelonephritis in Children 10 and Under, Massachusetts General Hospital, 1948–1956

No of Cases	Cured	Not Cured	Died*
61	58 (95 0%)	3 (5.0%)	2 (3.2%)

* Both children died from severe renal infections:
B proteus and *B. proteus* and *B. pyocyaneus* were the invading organisms

These figures illustrate the excellent immediate results of the treatment of acute pyelonephritis in children. Very likely there were some relapses in these cases where long-term follow-up was not possible. Cases that had repeated acute infections are classed as chronic pyelonephritis.

Chronic pyelonephritis in children is a difficult disease to treat successfully. In spite of adequate initial antibacterial treatment and meticulous examination, the disease has been persistent or recurrent in many instances Successful control of infection often seemed to be reached only to be interrupted by other episodes of chills and fever, sometimes while on a prolonged course of treatment.

When vesico-ureteral reflux was present the infection almost always resisted antibacterial therapy. To correct reflux, various operations have been designed One of the most successful has been re-implantation of one or both ureters in a submucous tunnel. This operation has eliminated reflux and has usually resulted in an improvement to a damaged upper urinary tract and cure of the infection.

A 2-year-old female infant, with repeated attacks of acute otitis media caused by a staphylococcus infection, developed pyuria, chills, and fever Cultures of the urine grew. *S. albus*, beta hemolytic streptococci, and finally *B. proteus* Many antibiotics failed to eliminate the urinary tract infection.

The bladder and urethra were normal by panendoscopic examination The left kidney was normal by intravenous pyelography. The

right kidney had good function but the superior calyx was dilated and irregular. A right retrograde pyelogram confirmed this finding (Fig. 69, A). A cystogram demonstrated vesico-ureteral reflux up a dilated right ureter (Fig. 69, B).

The right ureter was reimplanted into the bladded by a submucous tunnel. The right ureterovesical reflux was cured and the severe infection was controlled (Fig. 69, C) although two years after operation there was reflux up the left ureter. If this results in symptoms it is planned to reimplant the left ureter.

The operative technic has been well described by Politano and Leadbetter (18).

Unless obstructions to the free flow of urine are corrected the chance of curing infection is slight and one can expect recurring attacks of pyelonephritis with progressive damage to the kidneys.

In the lower urinary tract, narrowings of the vesical outlet may be corrected by transurethral resection or by plastic operations on the bladder neck (see Fig. 68). Posterior urethral valves may be similarly removed. Strictures of the urethral meatus are easily cured, not by dilatation, but by a minor plastic repair. In the upper urinary tract, obstructive lesions that require correction are strictures of the ureter, aberrant blood vessels that cross the ureter, and the many abnormalities of development of the kidneys (19).

As in chronic pyelonephritis in adult life, these cases in childhood were divided into complicated and uncomplicated cases. The cure rate for both groups was approximately the same and not very high when the usual ability that children have to recover from illness is considered. The seriousness of chronic renal infection in the early years of life is illustrated by the fact that 10 per cent of these children died in uremia (Table 13).

Prognosis

The chance of cure of acute pyelonephritis in childhood is excellent as shown in Table 12. However, these figures were based upon cases of one or more episodes of acute infection that were promptly cured. The figures do not take into account the cases of acute pyelonephritis that kept recurring in spite of adequate

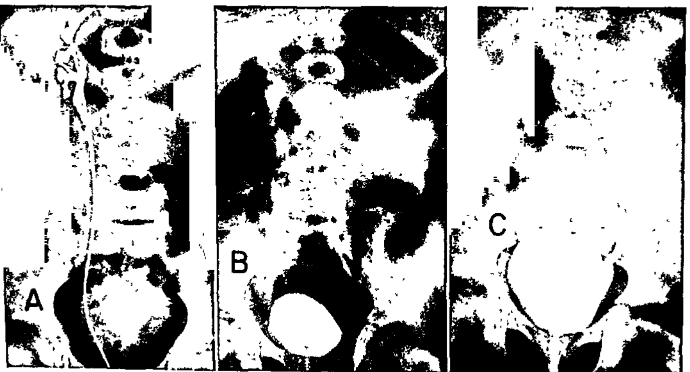


FIG. 69. Vesico-ureteral reflux and chronic pyelonephritis. A. The superior calyx of the right kidney is dilated and irregular. Retrograde pyelogram. B. Reflux up a dilated right ureter. Cystogram. C. Result 2 years after reimplantation of right ureter. The right ureterovesical reflux has been cured. Reflux now is present on the left side, but there are no symptoms. Cystogram.

TABLE 13

Chronic Pyelonephritis in Children 10 and Under, Massachusetts General Hospital, 1948–1956

	No of Cases	Cured	Not Cured	Died in Uremia
Complicated	28	10 (35.7%)	18 (64.3%)	4 (14.3%)
Uncomplicated	37	15 (40.6%)	22 (59.4%)	3 (8.1%)
Total	65	25 (38.4%)	40 (61.6%)	7 (10.4%)

and prolonged therapy. Such cases are considered to be chronic pyelonephritis.

The prognosis of chronic pyelonephritis is most uncertain for although about one-third might possibly be cured, nearly two-thirds could not be cured. About 10 per cent died in uremia from advanced renal damage. Many of the cures of complicated chronic pyelonephritis resulted from corrective surgical procedures. In most of the uncomplicated cases this was not possible and in well over one-half of such cases antibacterial treatment failed (20).

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9

PYELONEPHRITIS AND DIABETES

Renal infection often occurs in diabetic patients and this complication may be serious. Resistance to any infection is less in diabetics than in well individuals and infection in the kidney may be severe, rapidly progressive and, at times, fatal, especially when pyelonephritis is acute and associated with diabetes. An especially dangerous and frequently fatal form of this disease in necrotizing renal papillitis. The symptoms of kidney infection in diabetes often are vague and misleading and many times have been wrongly attributed to the diabetic state. Treatment is notoriously unsatisfactory and cure is difficult to attain. Pyelonephritis is a chief factor in the death of many diabetic patients.

A 49-year-old diabetic woman was admitted to the hospital ward from the Out-patient Department because of a persistent urinary infection. This had not responded to treatment with many drugs. Her diabetes was well controlled. Urinary symptoms were insignificant.

The fasting blood sugar was 170 mg. per cent. Blood pressure, 130/90. Urine: specific gravity, 1.013, albumin, 2 plus, sediment,

many W.B.C P S P. test, 60 per cent in two hours. Urine culture, *E coli* sensitive only to chloramphenicol This drug failed to eliminate the infection

An intravenous pyelogram was made. Total renal function was good The left kidney was normal in appearance. The right kidney was obviously diseased with marked caliectasis (Fig. 70).

The right kidney was removed and, although the patient felt well, *E coli* persisted in the urine cultures.



FIG. 70 Diabetes and chronic pyelonephritis. Persistent *E. coli* infection. Normal left kidney. Right hydronephrosis Right nephrectomy. Intravenous pyelogram.

The pathological report was chronic pyelonephritis and hydronephrosis. Marked intimal thickening of the arteries was present

The case illustrates the difficulty of eradicating urinary tract infection in the diabetic

Pathology

Significant infection of the urinary tract was found present at postmortem examination in 30 per cent of diabetic patients at the New England Deaconess Hospital (1) (Fig. 71) Many of these patients presented a distressing picture of advancing pyelonephritis with renal or perirenal abscesses, degenerative vascular lesions, and renal failure Pyelonephritis was found at autopsy in 18 to 20 per cent of diabetics by Joron *et al* (2), a considerably higher incidence than occurs in the general population Acute pyelonephritis was given as the cause of death in 7 3 per cent of



FIG. 71 Diabetes Acute and chronic pyelonephritis. Diffuse cellular infiltration There are no specific renal changes characteristic of diabetes Photomicrograph Low power

307 autopsies on diabetic patients by Robbins and Tucker (3). This is in contrast to figures of 1.3 per cent in nondiabetics.

In some patients with a long diabetic history, a deposit of hyalin material is formed between the glomerular capillary loops with all or most of the glomeruli involved and some to almost complete obliteration. This condition was described in 1936 by Kimmelstiel and Wilson (4) (Fig. 72). It frequently is accompanied by massive albuminuria, edema, nitrogen retention and hypertension (5). This lesion has been said always to be associated with some degree of pyelonephritis

A striking feature of autopsy material on diabetic patients has been the presence of marked kidney or bladder inflammation in cases who have had diabetes for a relatively short time. The increased susceptibility of the diabetic to infection, *therefore*, must originate soon after the onset of the disease (6).



FIG 72 Diabetes and pyelonephritis. Kimmelstiel-Wilson glomerular sclerosis and severe chronic pyelonephritis Diabetic nephropathy. Photomicrograph. Low power.

The histological renal lesions of pyelonephritis in diabetics, in other respects, are similar to those described under acute and chronic pyelonephritis.

Bacteriology

Many different organisms are implicated in the diabetic with pyelonephritis. The commonest is *E. coli*, but mixed populations of bacteria occur with considerable frequency. Staphylococci often are present with *E. coli* and are apt to come from septic foci such as furuncles, carbuncles, or other suppurative lesions. *A. aerogenes*, hemolytic and nonhemolytic streptococci, *B. proteus*, and *B. pyocyaneus* may be encountered in severe infections of the kidney.

The bacteriology of 127 cases of pyelonephritis in diabetics at the Massachusetts General Hospital is given in Table 14.

The most frequent organism isolated in pure culture in our diabetic patients with pyelonephritis was *E. coli* (Fig. 73). This was true in about 40 per cent. Mixed bacterial populations occurred with more frequency (53 per cent).

A woman of 33 with severe diabetes was seen first 30 years ago. At that time, her complaints were progressive loss of weight, polydypsia, and polyuria. Her blood sugar was 228 mg. per cent, with glycosuria and a blood pressure of 110/70. During the next 14 years she had many hospital admissions for cellulitis, superfi-

TABLE 14

Bacteriology in Diabetes and Pyelonephritis, Massachusetts General Hospital, 1948-1956

Organism	No. of Cases	Per Cent
E. coli	50	39.3
Staphylococci	2	1.6
Streptococci	3	2.4
B. proteus	1	0.8
Mixed	68	53.5
No growth	3	2.4
Total	127	100



FIG 73 Diabetes and pyelonephritis *E. coli* infection. The left renal pelvis and calyces show the effects of chronic infection. *Lateral retrograde pyelogram*

cial abscesses, and sinusitis. The diabetes was poorly controlled in spite of careful treatment

In 1946 she first had acute pyelonephritis with *E. coli* and *B. proteus* cultured from the urine. Renal studies at this time showed dilatation of the left ureter and left renal pelvis and a small right kidney with poorly filled calyces (Fig 74).



FIG 74 Diabetes and chronic pyelonephritis Mixed infection Although renal function is good, both kidneys show the changes of chronic infection The right kidney is small and the calyces are not well filled The left kidney pelvis and ureter are dilated and some calyces are distorted Intravenous pyelogram

The urinary infection responded to streptomycin temporarily Attacks of pyelonephritis resumed, however, with *E coli* persistently cultured from the urine Each attack of pyelonephritis could be controlled for a time by streptomycin

In 1952 the blood pressure had risen to 150/100 She was weak

and short of breath Blood sugar, 342 mg. per cent. The eye grounds showed early retinal changes. The left kidney pelvis now was dilated. Vision became blurred from diabetic retinopathy. She has continued to have *E. coli* in the urine up to the present time in spite of persistent drug therapy

In these mixed infections, *B. proteus* was present in 27 cases (21.2 per cent) and *B. pyocyaneus* was found in 18 (12 6 per cent). These resistant organisms probably were factors in the high mortality and the poor results from treatment in our diabetic patients who had pyelonephritis.

Symptoms

A complete lack of symptoms referable to the kidney has been a feature of pyelonephritis in the diabetic patient. The renal lesions found at postmortem examination often have been out of proportion to the symptoms. In many patients, there has been nothing to suggest infection of the kidneys. Frequent and uncomfortable urination, if present, in many instances have been attributed to the diabetes. Even in acute pyelonephritis the usual symptoms of acute renal infection may be absent or misleading

In these acute renal infections there may be only vague abdominal pain and tenderness but the tenderness often is not in the costovertebral angle. Other symptoms of acute pyelonephritis in these patients are fever, chills, nausea, vomiting, drowsiness, and prostration. Acidosis and vomiting with ketonuria has been ascribed to the diabetes when it really was caused by chronic pyelonephritis and renal failure. The outstanding symptoms, at times, have strongly suggested gastrointestinal disease, and since urinary symptoms were absent, pyelonephritis was not suspected.

In 1 or 2 per cent of all diabetic patients neurogenic bladder dysfunction occurs as a complication. *This results from a degeneration* of nerve fibers. Patients afflicted with such a disorder complain of difficult urination or even complete urinary retention. This complication may lead to serious infection of the urinary tract with irreversible changes in the bladder and kidneys, uremia and death (7).

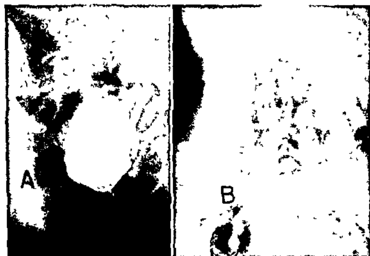


FIG. 75 Diabetes, neurogenic bladder, and chronic pyelonephritis A. Atonic, trabeculated bladder with left vesico-ureteral reflux Cystogram B Bilateral hydronephrosis and hydro-ureters Intravenous urogram

A 74-year-old woman and a severe diabetic was admitted in urinary retention

The urine was heavily infected, *E coli*, *B pyocaneus* and *B proteus* were cultured

A cystogram demonstrated a dilated bladder with trabeculation and left ureterovesical reflux (Fig 75, A) Both kidneys and ureters were dilated by intravenous urography (Fig 75, B)

The ureters were transplanted to an isolated segment of ileum but the patient died soon after operation Death was largely due to severe chronic pyelonephritis in a diabetic

Since the development of atherosclerosis is commonly accelerated in the diabetic patient, hypertension associated with pyelonephritis should be rather common This was true in our own patients, for hypertension was present in 50 or nearly 45 per cent of 127 patients who were diabetic The combination of hyper-

and short of breath. Blood sugar, 342 mg. per cent. The eye grounds showed early retinal changes The left kidney pelvis now was dilated. Vision became blurred from diabetic retinopathy. She has continued to have *E. coli* in the urine up to the present time in spite of persistent drug therapy

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FIG 76 Diabetes, hypertension, and pyelonephritis The hypertension was not controlled by sympathectomy Renal infection could not be eliminated The left renal calyces and ureter are dilated The right kidney is less affected Intravenous urogram

Roentgen examination also may be revealing by demonstrating differences in the size of the kidneys (Fig 77) If renal function is adequate, intravenous urography is indicated and is preferable to cystoscopic examination with retrograde pyelography because of the risk of introducing resistant organisms There are times,

tension and diabetes was a serious one for 28 or 36 per cent of our diabetic patients with hypertension died in uremia (8).

A 39-year-old diabetic woman with a blood pressure of 200/120 and apparently normal kidneys had a bilateral lumbodorsal sympathectomy. A renal biopsy at this time was reported nephrosclerosis grade two

After operation her blood pressure was somewhat lower (190/90) but it gradually climbed to 220/110 Several years later, she began to have attacks of acute pyelonephritis with chills and fever. *E. coli*, beta hemolytic streptococci and *S albus* were cultured from the urine.

An intravenous urogram now showed left renal caliectasis and a dilated left ureter. The right kidney was less affected (Fig 76)

Pyuria and positive urine cultures persisted in spite of intensive drug therapy.

The symptoms of cystitis with bladder irritability, frequent urination, dysuria, cloudy urine, and hematuria all deserve serious consideration in the diabetic.

Diagnosis

The complete absence of urinary symptoms that so often exists in diabetic patients with pyelonephritis often clouds the diagnosis Renal infection should be thought of in any diabetic who has an unexplained fever, regardless of immediate urinary findings This is particularly true if the diabetes is uncontrolled or inadequately controlled.

Fever, chills, nausea, vomiting, and drowsiness may signify kidney infection and impaired renal function. General physical examination often is unrevealing or there may be evidence of renal enlargement and kidney tenderness.

Urine examination is, of course, of importance. True infection is detected by pyuria or the presence of significant numbers of bacteria by culture or in the stained urinary sediment.

One is often surprised to find varying degrees of nitrogen retention in these patients who are active and seem to be well. The usual tests of renal function also may give evidence of serious and unsuspected degrees of renal impairment.



FIG. 76. Diabetes, hypertension, and pyelonephritis. The hypertension was not controlled by sympathectomy. Renal infection could not be eliminated. The left renal calyces and ureter are dilated. The right kidney is less affected. Intravenous urogram.

Roentgen examination also may be revealing by demonstrating differences in the size of the kidneys (Fig. 77). If renal function is adequate, intravenous urography is indicated and is preferable to cystoscopic examination with retrograde pyelography because of the risk of introducing resistant organisms. There are times,



FIG 77. Diabetes, hypertension, and chronic pyelonephritis A woman of 65 with right flank pain and hematuria. *E. coli* and *S. albus* urinary infection Blood pressure 190/90 The left kidney was normal. The right kidney is small with dilated and irregular calyces. Retrograde right pyelogram

however, when such a risk is justified since intelligent treatment is based upon an accurate diagnosis (Fig. 78).

As indicated, many diabetic patients have unsuspected infection of the kidneys. Any diabetic patient who is not doing well and whose metabolic disease is poorly controlled is a suspect for



Fig 78 Diabetes and chronic pyelonephritis Persistent urinary infection The right kidney is hydronephrotic and infected secondary to congenital stricture of the ureter Cured by right nephrectomy Bilateral retrograde pyelograms

a renal complication. If this is kept in mind, and early and vigorous treatment is instituted, many lives may be prolonged

Treatment and Prognosis

The treatment of pyelonephritis in diabetics has been notoriously unsatisfactory This has been our own experience (Table15)

TABLE 15

Treatment of Pyelonephritis in Diabetics, Massachusetts General Hospital, 1948-1956

No of Cases	Cured	Not Cured	Died in Uremia
127	17 (13.4%)	110 (86 6%)	35 (27.6%)

These figures tell the seriousness of pyelonephritis in diabetics. *The chance of cure was exceedingly small in our experience* (13 4 per cent). Over one quarter (27.6 per cent) of our diabetic patients who had pyelonephritis as a complication died in uremia.

Fourteen of these 127 diabetics (11 per cent) had acute pyelonephritis. Nine of these patients (64 3 per cent) were at least temporarily cured of their infection and five (35.7 per cent) were not cured. Three (21.4 per cent) died as a result of the renal infection. *There was, therefore, a much better chance of curing acute* pyelonephritis in these diabetic patients than when the disease was chronic, but with a much lower percentage of cures than in nondiabetic patients. The mortality of the acute infections (21.4 per cent), moreover, was *considerably higher* than in nondiabetics.

Bladder dysfunction in the diabetic has responded in some instances to prolonged catheter drainage together with the elimination of severe infection and control of the diabetes Removal of tissue from the bladder neck by transurethral resection has established normal voiding for some patients Cholinergic drugs occasionally are helpful.

Prolonged treatment with appropriate antibacterial drugs is generally advised for diabetics with pyelonephritis. Infections caused by *E. coli* alone often respond to adequate doses of the sulfonamides. Mixed infections are less likely to do well. The more resistant organisms such as *B proteus* or *B. pyocyaneus* may be inhibited by such drugs as Furadantin or chloramphenicol. Too often, however, the final result of intensive antibacterial treatment has resulted in the appearance of organisms that were resistant to all available agents.

Necrotizing Renal Papillitis

This is such an important renal complication in the diabet
that it deserves special consideration The condition has bee
termed renal medullary necrosis, necrosis of the renal papilla
renal papillary necrosis, and necrotizing pyelonephritis

Pathology

The actual pathogenesis of this condition is not too well unde
stood but it is believed to be the result of ischemic necrosis of th
renal papillae, accompanied by a severe inflammatory proce
caused by bacterial invasion Although it occurs in nondiabet
patients, usually associated with urinary obstruction necrotizi
renal papillitis most frequently is associated with diabetes Th
lesion may affect one or both kidneys It occurs in 3 to 5 per cen
of autopsies on diabetics.

The gross appearance is one of infarction of one or more of th
renal papillae The involved areas are gray or greenish yellow i
contrast to the color of the rest of the kidney substance The tip
or most of the papillae appear necrotic and with sequestratio
when the lesion is advanced

On microscopic examination, there is a complete loss of norma
architecture. Areas of coagulation necrosis involve one or mo
papillae. Infarcted areas are surrounded by a zone of dense in
flammatory exudate There is an intense cellular infiltration wit
polymorphonuclear leukocytes and mononuclear cells. Periphe
ally there is hyperemia and edema The diseased areas are sharp
demarcated from normal renal tissue (Fig 79) Acute pyel
nephritis may be present in the parenchyma of the kidney (9)

Symptoms

In the reported cases of necrotizing renal papillitis, sympton
have been variable In some instances, the diseased process ha
been acute and fulminating with signs of overwhelming seps
rapid and progressive renal failure uremia, and early death A
other times, renal infection is known to have been present fo
weeks or months with acute febrile episodes ending in oliguria an



FIG 79 Necrotizing renal papillitis and diabetes Junction zone of a necrotic papilla with the area of severe acute pyelonephritis. Photomicrograph Low power.

uremia Often, the signs and symptoms of necrotizing renal papillitis have given no hint of the real situation and the lesion has been found only at postmortem examination.

Oliguria and anuria have not been prominent symptoms except terminally. Occasionally, hematuria has occurred accompanied by renal colic and the passage of blood clots

Diagnosis

Necrotizing renal papillitis is to be suspected in any diabetic who has severe acute pyelonephritis. In the past, an accurate diagnosis has been made more often at postmortem examination than at the bedside.

Certain features may suggest this disease in diabetic patients. Diabetics who are critically ill with chills, fever, and prostration are good candidates for necrotizing renal papillitis. Suspicion is strengthened when there is a leukocytosis of 12,000 to 30,000,

albuminuria, and pyuria. Urine cultures often show mixed infe tions such as *E. coli* and *B. proteus* or *E. coli* with staphylococci streptococci.

X-ray examination has been an aid, at times, in the diagnosi Early renal changes may be detected by intravenous or retrograd pyelography. Typically, they consist of ragged irregularities one or two calyces. Some dilatation of the calyces is present wit out any evidence of urinary obstruction. At times, the renal d formity has suggested malignant disease.

An important, although infrequent, diagnostic sign has bee the passage in the urine of a necrotic renal papilla. This did n occur in any of our own patients, but it has been reported and it does happen the diagnosis is clear.

Treatment and Prognosis

Many of the patients with necrotizing renal papillitis have di before effective treatment could be instituted. The best treatme is prophylactic. This implies good control of the diabetes, vigoro treatment of any infection of the urinary organs, and the corre tion of any obstructive lesions that may impede free urinary flo

If this lesion is suspected, immediate intensive treatment shou be started with the agent indicated by cultures of the urine a sensitivity tests. Often the real condition has not been suspect or the course of the disease has been so rapidly fatal that effecti treatment could not be instituted.

There have been a few reported instances of survival aft nephrectomy. Operation should be seriously considered on when it is certain that the disease is limited to one kidney a that its mate is uninvolved and shows no evidence of impairme of function. With a careful selection of cases, nephrectomy m be life saving.

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10

PYELONEPHRITIS AND PREGNANCY

Renal infection occurs frequently enough in pregnancy to warrant consideration. The physiological and anatomical changes in the urinary tracts of pregnant women make these structures particularly susceptible to infection. With present-day awareness of the likelihood of urinary infection during pregnancy and the effectiveness of the more recent antibacterial agents, pyelonephritis is seldom the serious complication that it was in former years. Although my hospital no longer has an obstetrical service, for completeness this brief chapter is devoted to pyelonephritis and pregnancy.

Practically all pregnant women have alterations from the normal in their urinary organs. These consist of some degree of ureteral dilatation chiefly on the right side and beginning above the pelvic brim (Fig. 80, A and B). Also present are hypertrophy of musculature with some edema and increased vascularity. These changes occur in the urethra, trigone, bladder, ureter, and renal pelvis (1). Such alterations usually take place after the third month of pregnancy and disappear several weeks after delivery.

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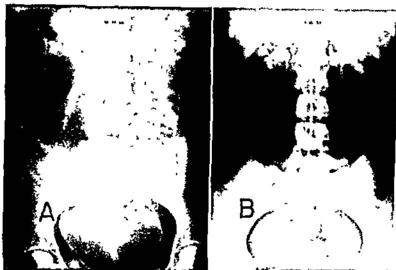


FIG 80 Pregnancy. A Physiological dilatation of both ureters and renal pelves and calyces in the eighth month. B Return to normal one month after delivery Intravenous urograms.

In spite of the fertile soil laid for infection by these anatomical and physiological departures from the normal, pyelonephritis occurs in only about 2 per cent of pregnant women (2).

The actual cause of these abnormalities during pregnancy has been debated for years with no conclusive answer of which I am aware It has been said that they occur because of hypotonia. The result is ureteral relaxation and impaired peristalsis. In normal pregnancy, there is normal ureteral tone and peristalsis until the fourth month. Then the ureter begins to lose these functions gradually so that by the sixth month tone and peristalsis have practically disappeared. During the last month of pregnancy they return and become normal about six weeks after delivery (3). Ureteral distention is accompanied by elongation and angulation of the ureters (4). Pyelonephritis occurs because of urinary stasis, the trauma of childbirth and infection (5). In 15,000 cases of pregnancy at the New York Lying-in Hospital the incidence of pyelonephritis was 2.02 per cent.

Bacteriology

The significance of bacteria in the urine of pregnant women has been the subject of considerable study. In normal pregnant women, bacteria were found present in the bladder urine in 43 of 114 cases before delivery and in 36 of 114 cases ten days postpartum. In 10 of 40 patients who had bacteria in the bladder urine bacteria were found also in the kidney urine (6). At the time of delivery, sterile bladder urine was obtained by catheter in 40 per cent of women and bacteria were present in 60 per cent. In 44 per cent the organism was *S. albus*. *E. coli* was found in 9 per cent. Only 2.5 per cent of these patients developed signs of a urinary tract infection postpartum (7). Others believe that most urinary infections start with *E. coli*. Many writers have described the presence of bacteria in the urine at the time of delivery.

The presence of only bacteria in the urine of pregnant women does not necessarily denote urinary tract infection. Doubtless, many of the organisms present were not pathogenic. Of more significance is the presence in the urine of known pathogenic bacteria, such as *E. coli*, together with leukocytes. More accurate information concerning urinary tract infection would be provided by such methods as quantitative bacterial counts using agar pour plates (8). Bacteriuria approximating 1000 viable organisms per ml. of urine was considered necessary for a certain diagnosis of infection. By this technic contaminating organisms are excluded. The presence of a moderate number of bacteria in the stained smear of the urine also suggests real bacteriuria (9). It seems to be true that low colony bacterial counts from urine obtained by catheterization represent urethral contamination (10).

Pathology

Again, it is questionable how bacteria reach the kidney in pyelonephritis of pregnancy. Evidence seems to be against an ascending route through the lumen of the ureter since reflux and antiperistalsis are said not to occur in pregnancy except in marked pathological conditions (11). Some writers believe that bacteria reach the kidney by the blood stream whereas others favor a

lymphatic route of extension although there seems to be no good evidence for the latter.

In the early stages of infection, the ureters and renal pelves become congested and edematous with an exudate over the mucosa. As the inflammatory process progresses the muscular and connective tissue layers become involved and peristalsis disappears.

On microscopic examination, there are acute inflammatory changes in the ureters and renal pelves with edema, cellular infiltration in the mucosa and submucosa and occasionally desquamation of the epithelium In limited areas, the inflammatory process extends through the entire thickness of the ureteral wall involving all layers and eventually leading, at times, to fibrosis and stricture formation (12).

Most of the substance of the kidney shows inflammatory changes with streaks of inflammation extending from the cortex to the renal pelvis. The interstitial tissue is infiltrated with round cells and polymorphonuclear leukocytes. The renal tubules are filled with pus cells In areas, there is almost complete destruction of the tubules with normal-appearing neighboring zones. The blood vessels are engorged Some of the glomeruli may show acute inflammatory changes. Abscesses may be present within the substance of the kidney. In postmortem examinations of 13 patients who died from pyelonephritis of pregnancy, Baird (13) reported that a constant feature was the presence of abscesses in the parenchyma of the kidney with only moderate dilatation of the ureter and renal pelvis.

In chronic pyelonephritis, the kidneys are small and shrunken with multiple scars on their surfaces There is massive destruction of the tubules, fibrosis of the glomeruli, round cell infiltration, and thick-walled blood vessels.

A woman of 23 had a normal delivery at the age of 17. During the pregnancy she complained of right flank pain which continued.

On examination, the blood pressure was normal. The urine was infected: albumin, plus 1; culture, *E. coli*.

The left kidney was normal The right kidney was small and all the calyces were dilated (Fig 81)

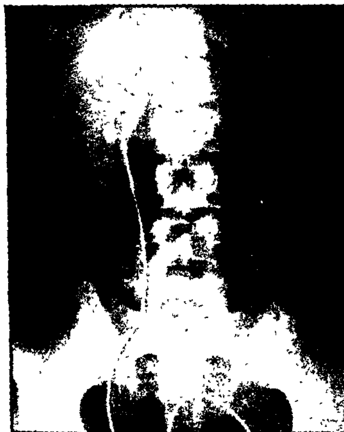


FIG 81 Pregnancy and chronic pyelonephritis Small, shrunken right kidney with dilated calyces Retrograde pyelogram

At operation, a 34-gm right kidney was removed Pathological report, chronic pyelonephritis Her symptoms disappeared and the urine became sterile

The gross and microscopic pathology of acute and chronic pyelonephritis of pregnancy are similar to that described in previous chapters

Symptoms

Acute pyelonephritis is most apt to occur in the latter part of pregnancy. Its onset usually is sudden in a patient who previously has been well. At times, there is a history of mild vesical irritability or hematuria but cystitis is predominantly a condition of the puerperium. Typically, the onset is heralded by severe pain in the flank, most often the right. This is accompanied by a marked elevation of temperature, septic in type, with chills, anorexia, and vomiting. Abdominal distention often is present. Right lower quadrant pain caused by the acutely inflamed ureter may suggest acute appendicitis.

Peters *et al.* (14) believed that pyelonephritis in pregnancy was a major factor in the production of toxemia. A high frequency of pyelonephritis in patients with toxemia of pregnancy, however, has not been confirmed by other observers.

Chronic pyelonephritis in pregnancy presents problems for the attending physician. Acute flare-ups of previous renal infections may be serious to both mother and child. Kidneys that have already been damaged during past pregnancies may not be able to withstand further insult. If, under these circumstances, pregnancy is to continue, frequent urine examinations, blood pressure readings, and tests of renal function are indicated. Indications for interruption of pregnancy have included those cases in which there has been renal damage from previous kidney infections to such an extent that a continuation of pregnancy is incompatible with maternal safety if the patient is allowed to go to term. Some patients with previously abnormal kidneys are such poor risks that they cannot tolerate pyelonephritis of pregnancy (12).

Infections of the urinary tract in the puerperium occur in approximately 1.5 per cent of deliveries (13). These may result from a continuation of pyelonephritis of pregnancy or from an exacerbation of chronic pyelonephritis. Postpartum bladder complications are a factor in these infections because of trauma to the bladder with residual urine or urinary retention (15). Bacteriuria is said to occur in 70 per cent of patients in the puerperium but only about 3 per cent develop cystitis (11).

Diagnosis

A diagnosis of acute pyelonephritis in pregnancy usually is readily made from the sudden onset and the characteristic symptoms of acute kidney infection Bacteriuria alone is not as significant as the presence of pus cells and bacteria in the urine Cultures of the urine will usually show *E coli* although staphylococci and streptococci may be present In severe infections there may be some degree of nitrogen retention

Abdominal symptoms may simulate appendicitis or acute cholecystitis The rapid respirations and rapid pulse rate may suggest pneumonia

During pregnancy, roentgen examinations are kept at a minimum. X-ray examination may be indicated, however, when the response to adequate treatment has been poor or when there is any reason to suspect that there may be a complicating lesion of the urinary tract such as calculous disease or some congenital abnormality

Cystoscopic examination may be necessary to make an accurate diagnosis. Until about the eighth month of pregnancy there should be little or no difficulty in catheterizing the ureters

Treatment and Prognosis

Previous to the days of effective antibacterial agents the treatment of pyelonephritis of pregnancy depended chiefly upon a high fluid intake and alkalinization of the urine. Fortunately most patients did well with these simple measures Catheterization of the ureters and irrigations of the renal pelvis sometimes were required in severe infections to tide the patients over to term

At the present time, most of these infections respond dramatically to treatment For immediate therapy the sulfonamides in doses of 2 gm four or five times a day are chiefly depended upon Since most urinary infections in pregnancy are from *E coli*, Furadantin mg. 100 four times daily often is used. The antibiotics, as a rule, are reserved for more serious or complicated infections and are selected by sensitivity tests.

In chronic pyelonephritis, treatment gives only temporary relief by controlling acute episodes of infection. To prevent irreversi-

ble renal damage in these cases it may be necessary to terminate the pregnancy.

After deliver, all symptoms usually stop abruptly and it is remarkable how the urinary tract returns to normal within a very few weeks If urinary drainage is unimpaired the inflammatory lesions will heal. Only in very severe or neglected instances will there be any permanent changes in the ureters or the kidneys. The chance of this taking place can be lessened by good antenatal care with frequent urine examinations. After delivery, treatment should be continued until repeated urine cultures give no evidence of infection. This applies particularly to infections in the puerperium where infected residual urine or urinary retention has necessitated intermittent catheterization or an inlying catheter.

If infection cannot be eliminated after delivery or during the puerperium, urological investigation should be undertaken to determine the cause.

Upper urinary tract infections in pregnancy may be a serious menace to mother and child. They may require skill in their recognition and sound treatment. Such patients should be in a hospital

The immediate mortality from pyelonephritis during pregnancy is not large. Over a 7-year period at the Boston Lying-in Hospital there were no deaths from this cause (12). In past years, others have reported a maternal mortality of 3.58 per cent and a fetal mortality of 15 8 per cent (3).

Diabetes and pyelonephritis in pregnancy is so serious that it has been considered a reason for terminating the pregnancy (16).

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11

PYELONEPHRITIS AND HYPERTENSION

A Russian-born laborer of 58 was seen in the medical Out-patient Department because of increasing dyspnoea for seven months. Previously well, except for generalized headaches for several years, he had always worked hard. For the past six months there had been anorexia, nausea and vomiting, vague abdominal pain and ankle-edema There were no urinary symptoms.

Upon admission to the hospital he was dyspnoeic The neck veins were distended T, 99°; P, 100; R, 25. The blood pressure was 205/120 Ankle edema was present and rales were heard at both lung bases The heart was enlarged by percussion and A_2 was accentuated. His breath suggested uremia. The retinal arterioles were narrowed, a few flame-shaped hemorrhages were seen but the discs were normal.

Blood chemistries Hgb, 10.5 mg per cent; W.B.C., 5000, normal differential N.P.N., 76 to 82 mg per cent; CO_2, 21.5; Cl, 109; Ca., 9.0, P., 6 Urine. specific gravity, 1.008; albumin, plus 4, sediment, R.B.C, W.B.C, and many granular casts; culture, no growth. P.S.P. test, less than 20 per cent in 2 hours. An electrocardiogram

was consistent with left ventricular hypertrophy The heart was considerably enlarged according to x-ray examination, and there was pulmonary edema

With sedation and digitalis he improved enough to leave the hospital but one month later he returned in a semi-comatose condition and died the same day

At postmortem examination, there was severe chronic pyelonephritis, cardiac hypertrophy and dilatation, secondary parathyroid hyperplasia, and generalized arteriosclerosis

Patients with hypertension have been divided into two classes (a) those with primary or essential hypertension, and (b) those with secondary hypertension. In essential hypertension no single cause for the high blood pressure can be demonstrated and this diagnosis is made by exclusion In secondary hypertension definite reasons for the elevated blood pressure can be detected although the actual mechanisms that cause the hypertension are not fully understood

Essential hypertension is a common condition Cases of hypertension where the causes can be recognized are much less common and some of these are renal in origin. This small component of the total number of cases of hypertension includes the cases in which we are interested Individuals with unilateral renal disease associated with hypertension may be of any age, the hypertension usually is of short duration, rapidly progressive, and of the malignant type. As a rule, these patients do not respond well to medical treatment but some of them have been relieved and perhaps have been cured by surgery (1).

Incidence of Hypertension

That hypertension is relatively common was shown by Puppel and Alyea (2) Of 65,479 hospital admissions 11 5 per cent had hypertension Only about 2 per cent of these hypertensive patients had surgical renal disease. Others have stated that approximately 10 per cent of hypertensive patients had demonstrable urological deformities with functional impairment (3)

Essential hypertension is low in incidence before the age of 20 and is present in about 25 per cent of individuals at 40 (4) It was

said also by Perera (5) that essential hypertension does not begin after the age of 48 or 50. The sudden onset of hypertension below the age of 20 or over the age of 50, therefore, should make one suspect that there may exist a known cause for the hypertension and that there may be a possibility of cure. Wakerlin (6) stated that less than 5 per cent of persons under 40 had hypertension and over 20 per cent aged over 40 years were hypertensive. Approximately 5 per cent have increased blood pressure on the basis of a known, although incompletely understood cause. The other 95 per cent have hypertension from unknown causes. The 95 per cent are the patients with essential hypertension (hypertensive vascular disease) Cases of renal hypertension are in the 5 per cent class

Other estimates of the incidence of hypertension in the general population, using a blood pressure of 160/90 as the upper limit of normal, have been made. Of 14,849 individuals 40 years of age or older, 41 per cent of males and 51 per cent of females were hypertensive according to Master and Marks (7).

Braasch *et al.* (8), in a study of 975 consecutive patients at the Mayo Clinic, reported that 25 per cent of patients who were 30 or more years of age had hypertension and that 60 per cent of elderly patients were hypertensive. They also stated that the incidence of hypertension in 1684 patients subjected to renal surgery was no higher than in a group taken at random. In a study of 264 patients with urological disease observed for over 15 years, Hines and Lander (9) found that the incidence of hypertension was practically identical with that of a control series of 790 patients who had no urological disease. Added to this, Homer Smith (10) believed that there was no convincing evidence that the already high incidence of hypertension was increased by urological disease. Unilateral renal disease might be the cause of hypertension in rare instances but the rarity of successes (19 per cent) coupled [illegible] disease does not caus[illegible] about this hypothes[illegible]t, he felt, upon conservative and recognized surgical indications, and not upon the hope of reducing blood pressure. If bilateral disease

is present, and it usually is present in advanced hypertension, nephrectomy might shorten life by removing an important fraction of total available renal function Baggenstoss and Barker (11) found an identical incidence of hypertension in patients with and without unilateral renal disease, 29 3 per cent and 29 0 per cent respectively.

Many observers have concluded that the incidence of urological disease is not greater in hypertensive patients than in normal individuals Pearman (12) found that in patients with urological evidence of pyelonephritis, the incidence of hypertension was no greater than in patients with no disease of the kidneys Goldring and Chassis (13) stated that 26 per cent of living patients had hypertension and that 24.2 per cent of 585 patients with unilateral renal disease had hypertension

Many years ago, Braasch and Jacobson from the Mayo Clinic reported that in 180 cases of bilateral chronic pyelonephritis hypertension was present in 26 1 per cent This was only 6 per cent more than they found in a control goup of patients In individuals less than 50 years of age, the incidence of hypertension was twice that of the control group The incidence of hypertension was said to be increased with an increase in the duration of symptoms and with the degree of renal deformity as shown by pyelography (14)

The incidence of hypertension associated with acute and chronic pyelonephritis in our own experience is given in Tables 16 and 17

Hypertension was uncommon (4.7 per cent) in our patients who had acute pyelonephritis and when present it usually occurred in elderly patients or in diabetics The incidence of hypertension associated with chronic pyelonephritis was higher (28 7 per cent),

TABLE 16

Acute Pyelonephritis and Hypertension, Massachusetts General Hospital, 1948-1956

Cases of Acute Pyelonephritis	No with Hypertension	Infection		Died in Uremia
		Cured	Not cured	
277	13 (4 7%)	9 (70%)	4 (30%)	2 (16%)

TABLE 17

Chronic Pyelonephritis and Hypertension, Massachusetts General Hospital, 1948-1956

Cases of Chronic Pyelonephritis	No with Hypertension	Infection		Died in uremia
		Cured	Not cured	
903	259 (28 7%)	28 (11.0%)	231 (89 0%)	90 (34.7%)

but this was scarcely higher than that reported by others for patients without renal disease. When chronic pyelonephritis was combined with hypertension, the infection was controlled in only 11 per cent of our patients and the deaths in uremia were 34.7 per cent

All of the foregoing reports indicate that hypertension is relatively common in the general population. It is low in incidence below the age of 20 and becomes more common at 40 to 50 years of age. A sudden onset of hypertension in individuals under 20 or over 50 suggests that the high blood pressure may be renal in origin. A close association between hypertension and the various forms of renal disease is held by many to be doubtful. This would seem to apply to *all* patients with hypertension and to *all* of those with diseased kidneys. Unilateral renal disease associated with hypertension is discussed later.

Renal Causes of Hypertension

For a long time it has been known that hypertension may be associated with certain renal lesions with sufficient frequency to seem significant although the reason for this was not at all clear. Examples are blood pressure elevations in polycystic kidney disease, glomerulonephritis, pyelonephritis, advanced renal tuberculosis, some renal tumors, and other conditions in which there had been a considerable degree of destruction of kidney tissue (Fig. 82). Obstructions of the lower urinary tract of long duration frequently were associated with elevations of the blood pressure and with relief of the obstruction the blood pressure levels returned to normal. In cases of prostatic enlargement, when this

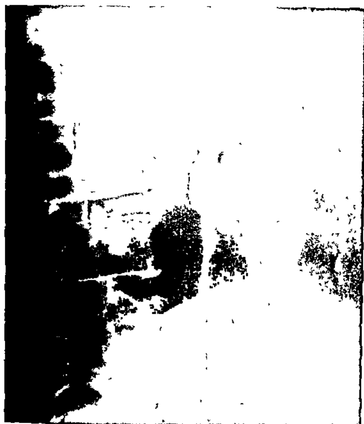


FIG 82 Multiple renal cysts and hypertension A man of 59, blood pressure 180/100 Left nephrectomy resulted in a relief of the hypertension Oblique left retrograde pyelogram

took place, it was considered to be a favorable time for operation Most of these renal lesions associated with hypertension involved both kidneys The experiments of Goldblatt stimulated interest in the renal origin of hypertension and contributed to a better understanding of the cause of certain kinds of hypertension

The concept of a relationship between renal ischemia and hypertension was of considerable importance, as Boyd (15) stated

The final proof of the effect of renal ischemia on the blood pressure was provided by the work of Goldblatt *et al.* in 1933 (16). Renal ischemia in dogs was produced by slowly narrowing the lumens of both renal arteries by means of adjustable clamps with resulting sustained hypertension. The same result was obtained by the complete constriction of one renal artery and removal of the opposite kidney. Blood pressure elevation was only transient when one renal artery was constricted and the opposite kidney was intact It was believed, that as a result of renal ischemia, a pressor substance was produced, but if a normal kidney was present this substance had no effect. Another possibility was that the pressor substance was neutralized by something produced by the intact kidney (Fig. 83).

Most investigators have agreed that a chemical substance of renal origin is the probably cause of the elevated blood pressure in experimental renal hypertension. By many, renin has been the accepted name of this chemical agent. Page (17) believed that renin, produced by an ischemic kidney, by itself was not a pressor agent but that renin required activation by hypertensinogen, a plasma globulin, the precursor of angiotonin The resulting substance, hypertensin (or angiotonin, a polypeptide), was the pressor agent Hypertensin was said to be destroyed by the enzyme, hy-

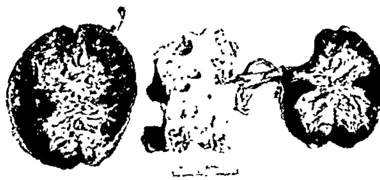


FIG. 83. Goldblatt kidney. A woman of 86 with partial atherosclerotic occlusion of the right renal artery. Blood pressure, 180/110. Long-standing hypertensive heart disease Autopsy specimen

pertensinase, which was produced in normal renal tissue Therefore, hypertension could result from an overproduction of hypertensin or from a lack of hypertensinase. No theory in this regard has been proved or generally accepted.

Pathology

Chronic pyelonephritis has been regarded as a lesion of primary importance in malignant hypertension (Fig 84) There seems to be good evidence that in children there is a relationship between chronic pyelonephritis and hypertension since hypertension is uncommon in the young and pyelonephritis is not at all uncommon When pyelonephritis and hypertension occur together, it has seemed probable that renal ischemia was the important factor in the elevated blood pressure (15)

Most writers agree that arterial changes in the kidney have an important bearing on the genesis of hypertension At the present



FIG 84 Severe bilateral chronic pyelonephritis with hypertension Extensive renal scarring, glomerular hyalinization and focal chronic inflammation Photomicrograph Low power

time, most evidence seems to implicate pyelonephritis and various vascular lesions as the two main causes of renal hypertension (4). Conditions that affect the main blood supply to the kidney are well established causes of renal hypertension.

The fact that chronic pyelonephritis may lead to arterial hypertension and to renal and cardiac insufficiency was pointed out by Weiss and Parker in 1940 (18). Their description of the gross and microscopic changes in the kidney was an outstanding contribution. Vascular lesions in chronic or healed pyelonephritis were prominent and they involved both the interarcuate arteries and the arterioles of the kidney. They described an increase of connective tissue in the intima of the arteries. The elastic membrane often was duplicated. The walls of the arterioles were thickened from a concentric proliferation of the cells. Arteriolar necrosis and acute arteriolitis resembling peri-arteritis nodosa, at times, were present. These vascular changes in pyelonephritis were said to be proliferative rather than degenerative. A single common feature described by many other writers was arterioloneerosis (Fig. 85).

The pathological changes in the kidneys of patients with so-called malignant hypertension and chronic pyelonephritis have been described more recently by Saphir and Taylor (19). A majority of the parenchymal changes in the kidney were similar to those described by Weiss and Parker (20). In general, the kidneys were smaller than normal and one kidney might be much more involved than its mate. The capsules stripped off with some difficulty leaving a kidney that was yellowish in color and with flat scars slightly depressed beneath the surface. These scars were more apparent on the cut surface. On section, the cortex was thinned and the normal architecture was obscured. The renal pelvis usually was slightly dilated and thickened. The tips of the pyramids were flattened. Abscesses were present only when there had been an acute exacerbation of chronic pyelonephritis.

Microscopically, the interstitial tissue was infiltrated with lymphocytes, plasma cells, histiocytes, and a few eosinophils. If the infection was in an acute stage, polymorphonuclear leukocytes predominated. In the healed stage, interstitial fibrosis was prominent and large numbers of lymphocytes were present. Changes

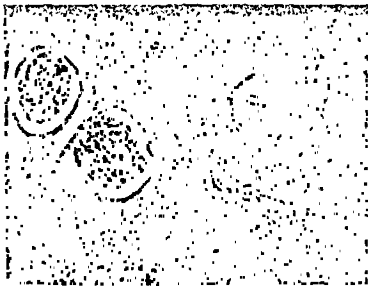


Fig 85 Chronic pyelonephritis and hypertension Extensive chronic inflammatory changes and moderate periglomerular fibrosis Photomicrograph Low power

in the tubules consisted of inflammatory cells within the lumens and small atrophic tubules The convoluted tubules and loops of Henle were dilated and had flattened epithelium Eosinophilic casts were in the lumens of the tubules When these casts were present in great numbers the dilated tubules filled with colloid resembled thyroid tissue A characteristic finding was concentric periglomerular fibrosis. Some glomeruli were fibrosed and hyalinized especially in scarred areas In general, however, the pathological changes in the tubules and in the interstitial tissue were more prominent than the changes in the glomeruli.

Severe vascular changes in the advanced stages of the disease were uniformly present Within the larger blood vessels there was intimal fibrosis or hyaline thickening with or without hypertrophy of the media. The lumens of the arteries became narrowed and deformed. The internal elastic lamina was thickened and might

be split into several isolated fragments. The same changes were present in the interlobar and interlobular arteries as were found in the arcuate arteries. Sclerosis of the arterioles was a uniform finding and there was a cellular onionskin-like proliferation of the walls of the vessels and marked narrowing of their lumens. Arteriolar necrosis was present in the glomerular capillaries and in the arterioles. Many of these changes were present only in patients *who had died in uremia and so were terminal in nature.*

After a review of the many reported cases of pyelonephritis with hypertension, the impression is gained that vascular changes within the kidney are more likely to be related to the elevated blood pressure than the pyelonephritis and that pyelonephritis without vascular changes probably seldom results in hypertension. The two may be closely related, however, in that the severe vascular changes with renal ischemia may be caused by the pyelonephritic process. Weiss and Parker (18) believed that the vascular changes in the kidney with pyelonephritis were a factor in the hypertension and that the factors responsible for [illegible] ular lesions were slow blood flow, intravascular [illegible]

who had normal blood pressures before operation, as reported by Friedman *et al.* (25).

Diseases of the Main Renal Artery

Although there has been some uncertainty about the relationship between hypertension and diseases of the renal parenchyma, it has been more evident that there is a close relationship between lesions of the main renal artery and elevations of blood pressure. Here, the experimental work of Goldblatt in dogs finds its counterpart in man by a reduction of the arterial blood supply to one kidney. Until fairly recently, interest in hypertension and renal disease was focused on such conditions as pyelonephritis as a cause of renal hypertension. When the disease seemed to be limited to one kidney, nephrectomy frequently was performed and the results often were disappointing.

> A woman of 30 came to the hospital because of severe headaches. At a previous admission $3\frac{1}{2}$ years before for ulcerative colitis, her blood pressure was 135/78.
>
> Now the blood pressure was 230/135. N.P.N., 27 mg. per cent. Urine: specific gravity, 1.021, albumin, 3 plus, sediment, a few R.B.C. and W.B.C., culture, no growth. There was cardiac enlargement and mild eye ground changes.
>
> By intravenous pyelography, the left kidney was small and its function was poor. The right kidney seemed normal. By translumbar aortography, the blood supply to the right kidney was normal. A very small renal artery supplied the small left kidney (Fig. 86).
>
> A left nephrectomy was performed. The kidney weighed only 25 gm. Nephrosclerosis, fibrosis and atrophy were present with arteriolar sclerosis.
>
> After operation there was no improvement in the hypertension and she was put on medical treatment.

Hypertension associated with renal artery lesions closely simulates experimental hypertension produced by partial compression of a main renal artery.

Compression or narrowing of the main renal artery occurs in a variety of conditions all of which may reduce the blood supply to the kidney. The renal artery may be compressed by neoplastic



FIG 86 Chronic pyelonephritis and hypertension Small left kidney. The blood supply to the right kidney is normal. The left renal artery is very small Left nephrectomy with no relief of the hypertension Lumbar aortogram.

disease primary in the kidney or by other retroperitoneal masses or inflammatory conditions. Extravasations of blood or urine may compress the renal blood supply by the resulting gradual fibrosis. Arteriosclerosis associated with chronic pyelonephritis, arteriosclerotic plaques with poststenotic dilatation, emboli, thrombosis, and stenosis from fibrous proliferation of the intima are some of the causes of narrowing of the renal artery.

of the first reported cases of hypertension caused by nar- of the renal artery and cured by nephrectomy was that of etter and Burkland (26) This occurred in a boy of 5½ years ad had an elevated blood pressure for almost two years At me of operation, his blood pressure was 170/110. Renal on was good and there were no eye ground changes After moval of a 100-gm pelvic kidney the blood pressure became l and remained so The main renal artery of the abnormal was partly occluded by a mass of smooth muscle

ny subsequently reported cases provide good evidence that oldblatt mechanism may occur in man (1, 4, 27–29)

1953 Burns (30) tried to find out why some of his patients ad pyelonephritis and hypertension were relieved of their lood pressure after nephrectomy and why others were not d. He found that in cases where the hypertension was re- there was severe sclerosis of the renal pedicle In the cases were not relieved the sclerosis was slight Occasionally, a t with sclerosis was not relieved. Burns felt that if the renal e was involved early, when functioning renal tissue was resent, hypertension would exist If the renal cortex was ed first and the renal pedicle later, the involved kidney no could produce hypertension

toms

ients with severe bilateral chronic pyelonephritis often have blood pressures (Fig 87) In unilateral chronic pyelone- s there may or may not be hypertension. Cases of severe pyelo- itis with associated hypertension average to be under 50 of age. Any history of previous urinary symptoms such as and fever, back pain, or pyuria seldom is given

asionally, hematuria is the first symptom in these patients ing may be severe and usually is from one kidney

The chief complaint of a woman of 60 was painless hematuria of o weeks duration There were no other symptoms

Her blood pressure was 210/110 The urine was concentrated to ly 1.010 and contained many R B C and albumin plus 4 Urine



FIG 87 Bilateral chronic inactive pyelonephritis and hypertension Both kidneys are small with compressed and irregular calyces. Intravenous pyelogram

cultures were sterile. Hgb., 14.0 mg; N.P.N., 25 mg. per cent; fasting blood sugar, 100 mg.

The left kidney showed minor changes by intravenous pyelography The right kidney excreted none of the dye At cystoscopic examination, indigocarmine appeared in ten minutes from the left kidney but none appeared from the right kidney.

By retrograde pyelography, the left kidney was large from com-



8 Hematuria with chronic pyelonephritis and hypertension is and diffuse caliectasis in the nonfunctioning, small right kid pensatory hypertrophy of the left kidney with some caliectasis de pyelograms

atory hypertrophy and there was a little dilatation of the renal s and calyces The smaller right kidney showed diffuse cali- is and pyelectasis (Fig 88)

uration of symptoms from the hypertension in favorable less than two years and often for only a few months

Characteristically, in the cases most susceptible to cure by nephrectomy, there is the sudden onset of an accelerated malignant type of hypertension. Headaches and eye ground changes are common Usually, these patients have no record of previous hypertension and the onset of the disease is not recognized until the symptoms of hypertension occur. This often ends in the rapid development of renal failure.

A 43-year-old woman came to the hospital because of severe dyspnoea At the age of 6 she was told she had kidney trouble but she felt well and went through three normal pregnancies with a normal blood pressure Six years ago on rountine physical examination for employment, she was told that her blood pressure was high. She continued to work, however, until 2½ years ago when she began to have exertional dyspnoea and frequent nose bleeds. Two years ago, her blood pressure was 210/100 She was put on antihypertensive drugs but did not do well There were no urinary symptoms.

Upon admission, her blood pressure was 240/138 The heart was enlarged and a grade 3 systolic murmur was present. The fundi showed advanced changes with old exudate. N P.N., 45 mg. per cent; Na , 138; Cl., 99, K., 4.1. Urine: specific gravity, 1 010; albumin, plus 2, sediment, many W B.C.; culture, *E. coli*.

By x-ray, the right kidney was small. At cystoscopic examination, indigocarmine was excreted poorly by both kidneys. The left renal pelvis was normal by retrograde pyelography. The right renal pelvis was large and the calyces were irregularly dilated. *E. coli* was cultured from both sides

The N.P.N. gradually rose to 210 mg per cent and within four months she died in uremia from chronic pyelonephritis

An analysis of 20 patients who had unilateral renal disease and hypertension relieved by nephrectomy was described by Perera and Haelig (31). None of their patients gave a history of hypertension of long duration. Infection was said to be responsible for the disease in the removed kidney. Other symptoms were headaches, convulsions, and eye changes with hemorrhages, exudates, and papilledema. They believed that the hypertension which accompanied unilateral renal disease was not only severe in in-

tensity but was of the accelerated or malignant type. The frequency of high diastolic blood pressure values, headaches, convulsions, and advanced retinopathy in almost all patients, except small children, supported their point of view The short history of illness suggested that the process was rapidly progressive. As a control group, there were 20 patients whose hypertension was believed to be on the basis of unilateral renal disease but whose blood pressures were not restored to normal following nephrectomy None of these patients had eye ground changes Over one-half had been hypertensive for over 4 years and the diastolic values in only 5 patients had been 130 or over Pyelonephritis was the diagnosis in only 5 of these patients, most of them had nephrosclerosis or congenital renal hypoplasia Perera and Haelig believed that the hypertension that accompanied unilateral renal disease was of an acute, severe, and rapidly progressive type The sudden appearance of high elevations of the diastolic pressures in older patients who previously had had normal blood pressures, they said, should make one suspicious of a definite cause for the hypertension and this might be an aid in the selection of candidates for nephrectomy. It was suggested that the hypertension of unilateral renal disease was different from that of hypertensive vascular disease and certain chronic kidney disorders and perhaps was related to the direct elaboration of a pressor substance against which no compensatory mechanisms had been established

In summary, hypertension often is present in patients with pyelonephritis The only symptoms usually are those caused by the hypertension and not symptoms related to the urinary tract When symptoms are of short duration, severe and rapidly progressive, attention should be focused upon unilateral renal disease as a possible cause of the hypertension If this is done, and the symptoms are carefully evaluated, some lives may be prolonged by proper treatment

Diagnosis

Of the many patients with high blood pressure, very few, perhaps 5 per cent, have hypertension from unilateral renal disease. Small as this number may be, it is important that they be identi-

it cannot be relied upon as an indication for nephrectomy for the relief of hypertension.

Renal Angiography and Aortography

Renal angiography, or renal arteriography, is the only accurate method of detecting abnormalities of the renal blood supply (32). Abnormal renal arteries and aneurysms of the main artery are plainly visualized by this method. With clear indications for its use and with technical experience, aortography with renal angiography has become a valuable diagnostic procedure

One of the most important applications of renal arteriography is in the diagnosis of occlusive lesions of the main renal arteries. The arteries may be compressed by extrinsic lesions, such as aneurysms of the abdominal aorta or of the renal artery itself, by renal or retroperitoneal neoplasms, or by organizing collections of fluid that may follow renal trauma. Intrinsic lesions of the arteries are emboli (Fig. 89), thrombosis, atherosclerotic plaques, and



FIG 89 Occlusion of the renal arteries by emboli An 84-year-old cardiac. Blood pressure 230/110 Abdominal pain and anuria. Areas of necrosis in both kidneys. Autopsy specimen.

congenital masses that occlude the lumen of the main renal arter
(33).

Indications for aortography as given by Poutasse and Dustar (29) are patients of any age with hypertension who have unexplained differences in the size of the two kidneys as shown by intravenous urography, *also patients who have a nonfunctioning kidney that has a normal retrograde pyelogram*. The latter has always been considered to be on the basis of a vascular lesion, arterial or venous.

Another group of patients in whom aortography is indicated

been hypertensive but whose disease becomes acutely more severe are considered to be candidates for aortography. Patients with hypertension that develops after an attack of pain in the flank should have aortography since the acute attack may be caused by thrombosis of a renal artery.

Intravenous urography and renal function may be normal even when unilateral or bilateral obstructive renal artery disease is present. There seems to be no doubt that lesions of the main renal blood supply may be a cause of hypertension.

In the differential diagnosis, Saphir and Taylor (19) believed that the blood pressure levels were higher in chronic pyelonephritis than in chronic glomerulonephritis and that the fairly constant anemia in chronic pyelonephritis distinguished this disease from nephrosclerosis.

Treatment and Prognosis

With patients who have hypertension and unilateral renal disease, the question naturally arises as to whether nephrectomy is or is not indicated. Past records show that, although there have been brilliant results in lowering the blood pressure and the relief of symptoms, there also have been many disappointments following nephrectomy. It is evident that each case must be very carefully studied before surgery is decided upon. The indications for

operation should be made more clear than has been true in the past.

When bilateral renal disease obviously is present nephrectomy is not indicated even if one kidney is much more abnormal than its mate. In such instances, *sympathectomy may be considered* but this operation is not always beneficial. Medical treatment may accomplish more as in the following case:

A girl of 10 had been well up to four months ago except for enuresis since the age of 3. She lost weight, had poor appetite, became pale, and often vomited. Headaches became severe and her vision became poor.

Upon admission to the hospital, her blood pressure was 240/190. The heart sounds were loud and a grade one systolic murmur was present. Urine: specific gravity, 1.003-1.008; albumin, 3 plus, sedi-

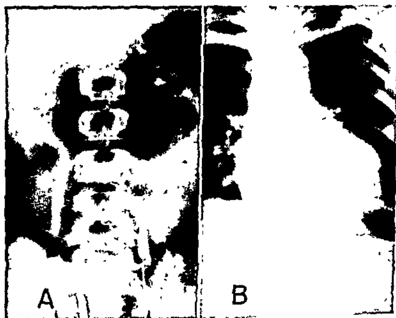


FIG. 90. Hypertension and bilateral pyelonephritis at 10 years of age. A. Both ureters are dilated, the renal pelves and calyces are dilated and renal function is impaired. Retrograde pyelograms. B. Left ventricular enlargement before treatment. (See Figs. 90, C and D).

ment, W B C , culture, *E coli* Hgb , 13 3 gm , N P N , 34 mg per cent, Na , 141, Cl , 100, K , 4 8, CO_2 , 29 4 Total protein, 5 7 P.S P. test, 45 per cent in 2 hours

Intravenous dye was excreted rather poorly by both kidneys and retrograde studies were made Both ureters were dilated and both renal pelves and the calyces of both kidneys were abnormal (Fig 90, A). Indigocarmine appeared from each kidney in ten minutes in only fair concentration Maximum urea clearance was 41 per cent of normal

A chest x-ray showed considerable cardiac enlargement (Fig 90, B) and an electrocardiogram was consistent with left ventricular hypertrophy The eye grounds showed papilledema and pinpoint hemorrhages

A benzodioxane test was negative On protoveratrine the blood pressure dropped to 170/100

The pros and cons of surgery were debated at length and it was decided to perform right and left lumbodorsal sympathectomies

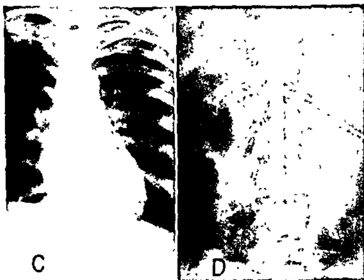


Fig 90 Hypertension and bilateral pyelonephritis at 10 years of age C Normal heart size 4 years later D Lumbar aortogram at the age of 20 Both renal arteries of normal size

Renal biopsies taken at operation were reported chronic pyelonephritis and nephrosclerosis grade four.

After operation, she was much better and for nearly four years her blood pressure ranged from 110/95 to 140/100. Then the blood pressure gradually rose to 183/130. She became easily tired, headaches returned and retinal hemorrhages appeared.

On reserpine she improved with low blood pressure readings (128/86–150/110) and she was symptom free. The heart was much reduced in size (Fig. 90, C).

At the age of 20 a lumbodorsal aortogram was made. Both renal arteries were of normal size (Fig. 90, D).

The renal lesions in which a decision for or against nephrectomy is likely to arise are when hypertension is associated with pyelonephritis and where one kidney is much smaller than its mate, one probable congenitally small kidney with a normal opposite kidney (Fig. 91), pyelonephritis associated with cal-



Fig 91 Congenital renal hypoplasia. Normal renal architecture and no inflammatory changes Photomicrograph Low power.

culous disease, hydronephrosis, and congenital abnormalities, and in any case where the symptoms and course of the disease suggest the possibility of a lesion of a main renal artery.

When hypertension exists and one kidney is small and the other kidney normal and there is no evidence of renal infection, the removal of the congenitally undeveloped kidney may or may not relieve the hypertension. There seems to be no method of determining whether the removal of the atrophic organ will or will not reduce the elevated blood pressure before operation. The following case is an example.

A 24-year-old woman was carefully studied because of high blood pressure Four years before, her blood pressure was known to be 134/32 Two years later it was 160/100 and she had severe headaches

Upon admission to the hospital her blood pressure was 170/100 The fundi were normal N P N , 19 mg per cent Normal blood chemistries Urine specific gravity, 1 020, albumin, 1 plus, sediment, few granular casts, culture, no growth Urea clearance, 60-73 per cent of normal Right kidney urine Na , 45 meq L , N P N , 104 meq L Left kidney urine Na , 65 meq L , N P N , 44 meq L Cultures, no growth

By intravenous pyelography the right kidney seemed to be normal The left kidney was small and had a bifid ureter (Fig 92, A) The heart was enlarged by X-ray (Fig 92, B)

The left kidney was removed Pathological report weight, 25 gm There was no evidence of pyelonephritis There was intimal proliferation of the renal arteries Diagnosis congenital renal hypoplasia

After operation, the blood pressure remained elevated She was given hypotensive drugs, felt better and the heart became reduced in size (Fig 92, C) Eighteen months after operation she became pregnant. The blood pressure was 200/100 and at seven months she delivered a macerated fetus

Although it seems certain that hypertension can result from renal disease, the actual mechanism by which hypertension is produced and the substance that is responsible for its production are unknown. Until these and other problems are better understood the indications for operation will remain uncertain.

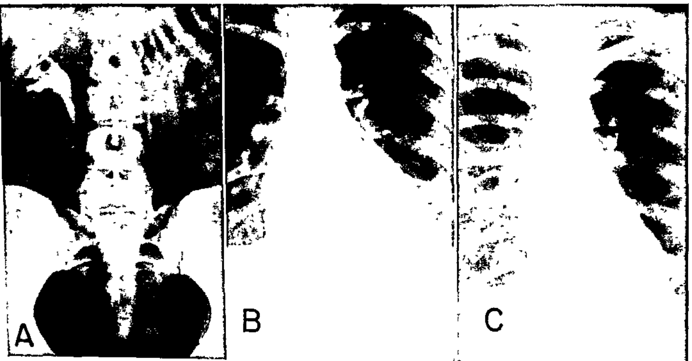


Fig. 92. Congenital renal hypoplasia and hypertension. A. Normal right kidney. Small left kidney with bifid ureter. Intravenous urogram. B. Left ventricular hypertrophy. Blood pressure, 170/110. C. Less cardiac enlargement after medical treatment.

It is generally agreed that surgery is not advisable in the [cut off] ence of bilateral pyelonephritis. When one kidney is smaller t[cut off] the opposite kidney and there has been progressive shrinkag[e] the kidney, the decision for or against removal of the small py[e] nephritic organ is difficult. Chronic pyelonephritis is more lik[e] to be bilateral than unilateral and although one kidney seems be normal, by all available tests, pyelonephritis still may [b]e present in the normal organ and nephrectomy will accomplis[h] nothing and may do harm. Our own experience in this situation has been disappointing although others have reported successes.

A woman of 27 was admitted to the hospital because of essential hypertension. For nine years she was known to have had high blood pressure. Frequent severe headaches now were present. The blood pressure had been 200/135 but during the next two years it gradually rose to 300/100.

At her second admission, an intravenous urogram showed a questionably normal-appearing right kidney and a small left kidney with dilated calyces (Figure 93). Urine: specific gravity, 1.025; albumin, 4 plus; sediment, hyaline and granular casts and many W.B.C.; culture, no growth. N.P.N., 44 mg. per cent. Urea concentration test, 38 per cent of normal. P.S.P. test, 45 per cent in 2 hours. Cl, 98; Na, 139; K, 3.6; CO_2, 30. Benzodioxane test negative. The heart was enlarged.

On fundoscopic examination, there were papilledema and flame-shaped hemorrhages. An abdominal aortogram failed to visualize the renal blood vessels.

The small left kidney was removed. It was atrophic and weighed only 32 gm. There was marked intimal thickening of the larger arteries. The arterioles showed intimal proliferation and the hyaline changes of severe nephrosclerosis.

After operation there was no improvement in the hypertension. Her condition grew worse in spite of medical care and she died within a month after surgery.

At postmortem examination, the right kidney showed malignant nephrosclerosis. The heart weighed 450 gm.

The sudden appearance of a progressive hypertension in in-[di]viduals who are known to have had a previously normal blood



FIG 93 Unilateral renal disease and hypertension. Some right pyelectasis, with good renal function The left kidney is atrophic from chronic disease Left nephrectomy with no improvement in the hypertension Intravenous urogram

pressure has been given as an indication for nephrectomy but in our experience this has not always been true

A woman of 72 came to the hospital because of severe headaches and nausea. She had been perfectly well up to 2½ months before admission.

Her blood pressure on entry was 290/150 N P N, 40 mg per cent Urine: specific gravity, 1.012, albumin, plus 2, sediment, few R and W.B C., culture, no growth Hgb, 16 mg per cent Cl, 83 The heart was enlarged The fundi showed hemorrhages and exudate She was drowsy, lethargic and had a uremic breath

By intravenous pyelography, the right kidney seemed normal There was no dye excreted by the left kidney By retrograde examination, a small left kidney was visualized (Fig 94)

The atrophic left kidney was removed It weighed 52 gm The pathological report was nephrosclerosis grade 3 There was marked fibrosis and intimal proliferation of the intrarenal arteries and hyalinization of the arterioles. The major renal artery was not abnormal.

After operation there was no improvement in the hypertension

Congenital underdevelopment of one kidney with a normal opposite kidney has been considered to be a cause of hypertension Many such kidneys have been removed in the hope that the hypertension would be relieved. Our own experience in this regard also has been disappointing. Perhaps the good results following nephrectomy in these cases and in the shrunken pyelonephritic kidney have been where vascular changes in the renal blood supply were of an extreme nature, although this does not always seem to be true.

Hypertension associated with pyelonephritis and renal calculous disease, hydronephrosis and congenital abnormalities has, at times, been relieved by nephrectomy Perhaps the successes so achieved were because the blood supply to the diseased organ was impaired, particularly the blood supply of the main renal artery A more careful study of the main renal artery in such cases seems to be advisable There certainly are more cases of renal calculous disease and hydronephrosis with normal blood pressures than with hypertension. Our own experience in this regard has been indifferent. Nephrectomy in such cases should be based on sound surgical indications rather than for the possible relief of hypertension

The most spectacular results in the relief of hypertension from surgery have been in patients with demonstrable narrowing of the

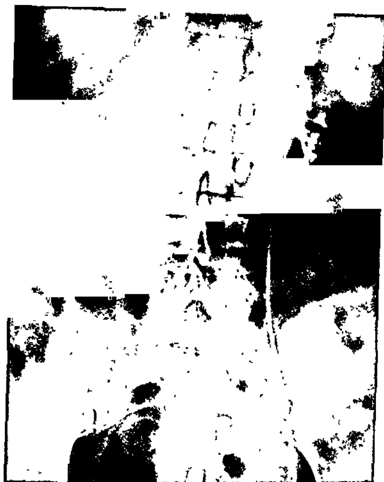


Fig 94 Unilateral renal disease and hypertension. Sudden onset of symptoms Normal right kidney. The left kidney had no function and was atrophic Retrograde pyelogram No improvement after left nephrectomy

renal arteries. At the present time, this can be detected only by aortography with visualization of the renal blood supply. Of 18 cases with unilateral narrowing of the renal artery studied by Oppenheimer, 83 per cent had hypertension. With unilateral hydronephrosis or chronic pyelonephritis, 32 per cent had hyperten-

sion, and with unilateral renal hypoplasia hypertension was present in 40 per cent. It was felt that there was no evidence that the last two conditions by themselves produced hypertension (27)

When hypertension and an obstructive lesion of a renal artery exist, the hypertension may be relieved and perhaps may be cured by nephrectomy, endarterectomy, with preservation of the kidney, or by an arterial graft. Such procedures have been performed successfully by Poutasse and Dustan (29) and by others

The following case is an example of renal artery disease associated with hypertension.

A 63-year-old paperhanger was admitted because of hypertension Four years previously, his blood pressure was known to be normal During the next three years it was 240/100 to 270 150 in spite of hypotensive drugs. Severe headaches and epistaxis developed

Upon admission, the blood pressure was 275/140 There was left ventricular hypertrophy and grade 3 eye ground changes Urine, specific gravity, 1 008, albumin, 0, sediment, many W B C and R B C and granular casts; culture, *B proteus* and *B pyocyaneus* Hgb, 12 0 gm Na, 140 meq L, K, 3 0 meq L, Cl, 94 meq L CO_2, 34. Serum creatinine, 1 8 meq L Regitine test negative Catechol amines normal. Creatinine clearance, 61 liters 24 hours

Roentgen examination. By intravenous pyelography the right kidney was normal but there was no left renal function Retrograde pyelography demonstrated an unobstructed left kidney that secreted no urine (Fig 95, A). A renal angiogram was made and the left renal artery was blocked near the aorta (Fig 95, B)

At operation, a flabby left kidney, gray in color, was exposed Within the left renal artery was an atheromatous plaque This was removed and the artery was repaired The kidney promptly became pink and firm and the blood pressure dropped to 120/80 Renal biopsy, severe atherosclerosis and moderate nephrosclerosis The left kidney again functioned.

His subsequent course for two months has been excellent with blood pressure readings of 150/80 and no symptoms Although he has not been cured of degenerative vascular disease, the relief of symptoms has been dramatic

Our own experience with nephrectomy for unilateral renal disease in an attempt to relieve hypertension is given in Table 18

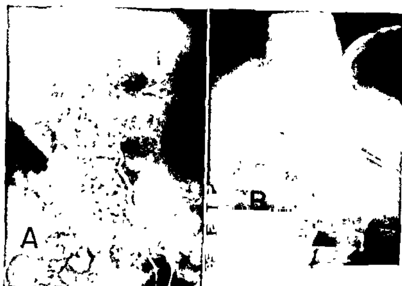


Fig. 95. Lesions of the main renal artery with hypertension. A. Nonfunctioning left kidney but with normal retrograde pyelogram B Lumbar aortogram The right renal artery is of normal size but slightly irregular The left renal artery stops abruptly near the aorta because of an atheromatous plaque Hypertension relieved by endarterectomy.

Table 18

Nephrectomies in Unilateral Renal Disease and Hypertension, Massachusetts General Hospital

Renal Lesions	Cases	Hypertension Relieved	Hypertension Unchanged
Calculous disease	6	1*	5
Hydronephrosis	5	1	4
Congenital renal aplasia	4	0	4
Chronic pyelonephritis with small kidney	2	1*	1
Renal cyst	2	0	2
Carcinoma of ureter	1	0	1
Total	20	3 (15%)	17 (85%)

* The patient with calculous disease and the patient with a shrunken pyelonephritic kidney, who were relieved of their hypertension, had severe narrowing of the renal artery.

Any discussion of the treatment of severe renal disease is not complete unless tribute is paid to the splendid accomplishments of the medical and surgical services of the Peter Bent Brigham Hospital. Renal transplantation has saved a number of lives already and doubtless will save many more (34)

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12

PYELONEPHRITIS AND THE UROLOGIST

Since pyelonephritis means that bacteria have gained access to the kidney, it is well to scrutinize how this may take place Any obstruction to the free flow of urine from the kidney to the external urethral meatus is a factor that favors infection Many of the obstructive lesions are congenital in origin Others are caused by calculous disease, neoplasms benign or malignant, trauma, and infection Our inability to treat chronic pyelonephritis as successfully as acute pyelonephritis perhaps is because of the presence of dilated renal tubules that are obstructed by cellular infiltration in the chronically diseased kidney and by areas of fibrosis in the interstitial tissue The urologist enters the picture for he is called upon to aid in the diagnosis and treatment of these conditions His responsibility is great for it is he who can introduce pathogenic organisms into a urinary tract that is free of infection This is one method by which infection may reach the kidney

Adequate studies of patients who have disease of the genitourinary organs is the basis of intelligent treatment No measure

have inlying catheters or drains, I believe, is wrong. Infections caused by bacteria that are sensitive to drug therapy often are converted to infections that are resistant to treatment. When the antibiotics are needed most for severe infections their effectiveness is lost. After all drains have been removed, intensive antibacterial treatment then is indicated and should be continued until all evidences of infection have cleared.

Although the urologist undoubtedly is responsible for some instances of urinary tract infection the risk of this can be lessened by careful technic, by the elimination of unnecessary instrumentation, by deferring certain procedures until the patient has been hospitalized, and by avoiding the unnecessary use of antibiotics.

Close cooperation between the Urological Service and other hospital services will result in better patient care.

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